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Opioids: psychological dependence, physical dependence and tolerance in cancer patients.

Statement of originality

This thesis is entirely my own work. All the studies included are original ideas.

Acknowledgement

Grateful thanks to Professor Geoffrey W. Hanks who made this work possible and who has a unique knowledge and understanding in this field.

Chapter 1

Introduction

The stimulus to embark on this thesis came from observation of the clinical challenges in effective cancer pain control, combined with the evidence for these challenges in the literature. Contrary to common beliefs, the difficulties in cancer pain management are not related to lack of understanding of pain mechanisms nor available treatments, rather the more common barriers are related to fear of opioids. Most patients diagnosed with cancer will require opioid analgesics at some time during their disease, and many will eventually require strong opioids.[1] In industrialised countries, 30-80% of cancer patients receive insufficient pain therapy, although physicians could ensure at least moderate pain relief for most patients by following the World Health Organisation (WHO) guidelines for treatment of cancer pain.[2-4]

The required dose of opioids is often underestimated. Physicians are concerned about serious side effects such as respiratory depression and addiction, and it has been shown that patients and their relatives not only share their physicians' concerns about addiction, but also are anxious about opioid efficacy during long-term treatment. Such concerns may lead to reduced patient compliance.[5]

Opioid drugs hold a paradoxical position in modern society. On the one hand they are recognised as the keystone to successful pharmacological management of cancer pain of moderate to severe intensity[7] and have an acknowledged role in the management of chronic non-malignant pain,[8] however on the other hand they are seen as drugs of addiction and abuse and have medical, legal or social consequences. There has been little contact between those who prescribe opioids for pain and those who deal with the consequences of abuse.

There are barriers to the appropriate use of opioids as analgesics: a fundamental problem is lack of understanding of commonly used terminology leading to misunderstandings, in relation to opioid analgesia[9] and another problem is fear of addiction and tolerance to opioid analgesia in both prescribers,

patients and carers.[10] These two problems are obviously linked in some cases. An important landmark study was carried out by Paice, Toy and Shott. This study examined the real factors associated with poor pain relief. Factors associated with higher pain intensity included the inpatient setting, the presence of metastatic disease, hesitancy in bothering the nurse, and concerns regarding tolerance and addiction. Although there was a strong relationship between concern about addiction and concern about tolerance, fear of tolerance appeared to have a greater effect on pain intensity scores than did fear of addiction.[10] The clinical implications are that these areas need to be addressed; we need more information, a consensus on these areas in pain management and effective education.

Tolerance is present when there is a need to increase the dose of a drug that is taken at a regular interval in order to sustain its initial effects. Tolerance does not usually develop to all of the drugs effects nor may it develop at a uniform rate with a specific drug. The precise mechanisms by which tolerance develop have not been completely defined. The multiplicity of opioid receptors and receptor subtypes (mu, delta, kappa and possibly others) and the limited knowledge of their coupling mechanisms underpin why cellular and biochemical changes underlying opioid tolerance and physical dependence remain poorly understood. Following chronic exposure to opioids, both down and up regulation of opioid receptors can occur, depending on the receptor type and/or the region examined.[11] As these changes generally appear after the tolerance is installed, they are unlikely to be responsible for it. However, opioid tolerance seems to be associated with some uncoupling (probably functional rather than physical) of the opioid receptors from G proteins normally associated with them, therefore resulting in a loss of the capacity of these proteins to exchange GDP for GTP.[12]

We know that clinically relevant pharmacological tolerance is not an issue in cancer pain management in the majority of cases. This has however not been carefully examined.

Physical dependence occurs as a consequence of exposure to a drug, resulting in physiological changes necessitating the continued presence of the drug to maintain normal function.[12] An increase in adenylate

cyclase activity, and therefore of cyclic AMP levels and certain protein kinase activities, have been claimed to be responsible for physical dependence in some cell types.[13] We know physical dependence may occur with the use of opioids as analgesics, however we do not know the prevalence.

Psychological dependence, or addiction which is a sociological term that has come to mean the presence of compulsive drug-seeking behaviour is usually accompanied by physical dependence and tolerance. The mechanisms of psychological dependence are complex and not simply associated with opioid use.[14, 15] However, physical dependence is not always accompanied by psychological dependence and it is this common misunderstanding that fuels fear of appropriate opioid use.

It is evident that these phenomena of tolerance, physical and psychological dependence are complex, however clarity of use of these terms is important, currently it is not optimal and this is confounded by a lack of systematic evaluation of these phenomena in pain patients. These are important barriers to good patient care.[16]

The aims of this thesis are to clarify beliefs in clinical practice about opioid dependence, both physical and psychological and opioid tolerance. The studies chosen as a means to this clarification are clearly clinical and I will divide them into the areas they cover.

The first study has the hypothesis: Patients with pain and who use opioid analgesia do not become addicted to opioids. To demonstrate this, 3 groups of patients had their patterns of opioid use compared: chronic cancer pain patients, chronic non-malignant pain patients and drug addicts.

The second study has the hypothesis: Patients with chronic cancer pain and with chronic non-malignant pain can use stable opioid doses over many months, even years, without needing to increase the opioid dose to maintain the same level of analgesia. This study addresses the question of clinically relevant pharmacological tolerance and was a follow-on study from the first study.

The third study addresses the question of physical dependence on strong opioids which clinically results in a physical opioid withdrawal syndrome on sudden discontinuation of opioids. The hypothesis is: Patients receiving a continuous intravenous infusion of diamorphine to treat painful mucositis post bone marrow transplant, can discontinue the diamorphine infusion abruptly when pain resolves, without developing a physical opioid withdrawal syndrome.

Clearly these three studies are linked: they address the three key areas of fear when using opioids; psychological dependence, clinically relevant pharmacological tolerance and physical dependence.

In addition to these key fundamental areas I examined important related areas. The first was the development of selective tolerance to the opioid side effect of constipation, and the relationship between opioid dose and constipation. The hypotheses were: (i) opioid dose is related to the degree of constipation and (ii) patients on stable opioid doses become tolerant to the constipation side-effect.

The final thread of the thesis is the complex question of whether morphine tolerance can be an important mechanism at spinal cord level, in patients with the clinical phenomena correlating to central wind-up. This specific mechanism of tolerance does occur in chronic pain and renders certain pains relatively unresponsive or completely unresponsive to morphine. This is clearly distinct from the general phenomenon of tolerance which is not clinically relevant in chronic pain management. The phenomenon of central wind-up which we know is mediated via the N-methyl-D-aspartate (NMDA) receptor is thought to be linked to morphine tolerance possibly via a nitric oxide synthetase mechanism. The result is pain with the specific features of allodynia, hyperalgesia and hyperpathia. This pain is classically morphine poorly-responsive or unresponsive. Animal studies have shown that NMDA antagonists such as ketamine can reverse this state.[6]

The hypothesis for the final study is: Patients on morphine but with clinical phenomena of central wind-up can have improved analgesia with the introduction of ketamine to their analgesic regimen.

Together, examination of these hypotheses is of direct clinical significance in cancer pain management, given that all the literature points to fear of addition and tolerance as the greatest barriers to cancer pain control on a world wide basis.

I had the great fortune to be guided by Professor Geoffrey Hanks (GH) in this thesis. He steered a group of experts in the fields of cancer pain (GH), addiction medicine (Professor Ghodse, St George's Hospital, London) and chronic non-malignant pain (Dr Amanda C de Williams, St Thomas's Hospital, London). I also had advice from Professor Michael Gossop, Addiction Medicine, Maudsley Hospital, London.

The largest part of the work for this thesis was carried out in St Thomas' Hospital (Oncology and Chronic Pain units) and in St George's Hospital (Addiction unit) London, and in the Bone Marrow Transplant Unit, Bristol.

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Chapter 2

Definitions, Clinical Relevance And Misconceptions

Tolerance, physical dependence and addiction:

Health care professionals, patients and families have exaggerated concerns about opioids and their potential side effects, in particular tolerance, physical dependence and addiction. Therefore it is critically important to understand the meaning of these terms and their clinical relevance to the management of cancer pain.

Tolerance

Definition:

Tolerance is a physiological state characterised by a decrease in the effects of a drug (e.g., analgesia, nausea or sedation) with chronic administration.

Clinical relevance:

It is important to distinguish between tolerance to analgesia and tolerance to side effects.

(1) Tolerance to analgesia.

Patients with unchanging pain can have a consistent level of pain relief from the same dose of opioids over time.[1-3] The need for higher doses of opioids is typically due to worsening pain and disease progression, rather than tolerance.

Tolerance to opioid side effects.

Tolerance usually develops to many of the side effects of opioids (sedation, nausea, itch) in a few days. The relationship between constipation and tolerance is very complex.

Misconceptions:

- To some, the need to increase the dose in response to the patient's report of pain is misinterpreted as a sign that tolerance may be developing. Unfortunately, this sometimes leads the physician to reduce the dose in a mistaken attempt to avoid or delay the development of tolerance. The appropriate response is to reassess the pain and increase the dose as indicated to relieve pain.

- Sometimes, to prevent the development of analgesic tolerance, opioids are administered at intervals which are too far apart to maintain continuous pain relief. This practice is inappropriate because it subjects patients to needless cycles of pain and pain relief.
- Often, health care professionals and patients are concerned about using opioids from the 3rd step of the WHO ladder, such as morphine, because of the mistaken belief that the medication will lose its analgesic effect; they want to save it until the pain is really severe.[4] This concern about analgesic tolerance is unfounded and can lead to inadequate pain management.
- Some health care workers and patients believe that using morphine for pain relief will suppress respiration and possibly cause death. In fact, clinically significant respiratory depression and sedation are very rare in cancer patients. This is because tolerance to the sedative effects of morphine develops rapidly, and because pain reverses morphine's depressant effects.[5]

Physical dependence

Definition:

Physical dependence is the physiological adaptation of the body to the presence of an opioid. It is defined by the development of withdrawal symptoms when opioids are discontinued, when the dose is reduced abruptly or when an antagonist (e.g., naloxone) or an agonist-antagonist (e.g., pentazocine) is administered.[6]

Clinical relevance

Physical dependence is a normal and expected response to continuous opioid therapy. Physical dependence may occur within a few days of dosing with opioids, although it varies among patients. Physical dependence (indicated by withdrawal symptoms) does not mean that the patient is addicted.[6]

Health care workers should advise patients to take their pain medication as directed, and that withdrawal symptoms may occur if they reduce their dose or stop taking the medication.[7] Symptoms of withdrawal may include agitation, insomnia, diarrhoea, sweating, and rapid heart beat. If the source of pain is successfully treated or removed, physical dependence is easily treated by gradually decreasing the opioid dose.

The development of physical dependence should not limit analgesic therapy. Antagonists and agonist-antagonists in the patient who is physically dependent should be strictly avoided because their use will neutralize the analgesic effect and cause a withdrawal syndrome. The prevalence of physical dependence is not known.

Misconceptions

- Physical dependence is frequently equated mistakenly with addiction. It is incorrect to use the term 'physical dependence' (a physiological state) to describe addiction (a dysfunctional psychological and behavioral syndrome).[1]
- Patients who express concern about physical dependence should be given correct information and reassured.

Addiction

Definition:

While tolerance and physical dependence are physical changes in the body, addiction is defined by aberrant changes in behaviour. Addiction is compulsive use of drugs for non-medical reasons; it is characterized by a craving for mood altering drug effects, not pain relief.[8] Addiction means dysfunctional behaviour, in sharp contrast to the improved function and quality of life that result from pain relief. Aberrant behaviours which indicate addiction may include: denial of drug use; lying; forgery of prescriptions; theft or drugs from other patients or family members; selling and buying drugs on the street; using prescribed drugs to get "high".[8]

Clinical relevance:

Addiction is extremely rare in cancer patients who use opioids for pain. Biochemical, social and psychological factors are more important in the development of addiction. Opioids should not be withheld for fear that a patient will become addicted. If a pain patient requests a strong analgesic, it is likely that the patient has inadequate pain control.

Misconceptions

- People who fear addiction, yet desire pain relief sometimes think "So what if I get addicted, I am going to die anyway."

- Patients and family members who express concern about addiction should be given correct information and reassured.

Pseudo-Addiction

Definition

Pseudo-addiction describes what happens when healthcare workers perceive as addictive behaviour a pain patient's requests for more or stronger pain medications. In fact, the patient's behaviour may be a response to inadequate pain management.[9] Pseudo-addictive behaviour is pain-relief seeking behaviour. Pseudo-addiction is an iatrogenic phenomenon, e.g. it is when problems result from the treatment efforts of health professionals.

Clinical relevance

Pseudo-addictive behavior may occur when analgesics are prescribed in inadequate doses or at dosing intervals that are longer than the duration of action of the drug.[7] Pseudo-addictive behaviors are more likely to occur in patient care settings where health care professionals are inadequately trained in pain management and the rational use of opioids. The appropriate clinical response to pseudo-addictive behaviors is to reassess the patient's pain and to treat the pain adequately.

Other terminology in this thesis

In addition to dependence and tolerance terminology clarification of the following three terms used to describe elements of neuropathic pain is necessary for complete understanding of this thesis.

Allodynia: pain to a stimulus which is usually non-painful e.g. light touch.

Hyperalgesia: increased pain to a painful stimulus.

Hyperpathia: prolonged duration of pain.

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Chapter 3

Do patients with pain become addicted to morphine?

Derivatives of the opium poppy have been successfully used for millennia for the desirable effect of pain relief and when used for the euphorigenic effects (which are not universal), they are generally being used for recreational purposes. While benefits have been universally recognised, the capacity of opioids to cause suffering has been equally appreciated through the course of history. [1] The status of opioids in medical practice has gone through cycles of favour to disrepute. [2] Medical practice with respect to the use of opioids for the treatment of pain has been heavily influenced by societal perceptions of addiction problems or psychological dependence and by laws controlling the use of opioids. Despite improving education the evidence exists to demonstrate that fear of producing addiction to opioids is foremost in the minds of most physicians when asked to provide medication for pain relief. This fear often interferes with their ability to provide adequate analgesia.[3]

One study demonstrates that those physicians who thought the probability of addiction was high after prescribing pethidine (meperidine) for ten days to a patient in pain were more likely to give lower initial doses, as well as to be less likely to respond to the need for increased medication with recurrent pain even if pain was due to terminal malignancy.[4] A second study of 100 patients with malignant pain found 60 per cent to be prescribed doses of pethidine of 50 mg or less, with 11 per cent having to wait for five or more hours before another dose with all prescriptions written for 'PRN' administration. [5]

In fact, the risk of initiating an addiction when opioids are prescribed appropriately for relief of pain is very small. Historical references attribute physicians as initiating dependence on opioids. Two early surveys (in 1925 and 1939) of addicts undergoing treatment reported that 9% and 4% respectively began their addiction with a medical prescription of an opioid drug for a painful disorder. [6] In 1954, a report noted that 27% of white male addicts and 1.2% of black male addicts began abuse as medical patients treated for pain. [6,7] Surveys of addicted populations are clearly subject to bias and a different

view has emerged from more recent data on medical patients who were assessed for the development of addiction after receiving opioids for the treatment of pain.

Another survey reviewing addiction among a population of black heroin addicts found less than 2 percent to attribute their addictions to prescription of an opioid for medical reasons. [8] Perhaps the largest survey of iatrogenic opioid dependence was done as part of the Boston Collaborative Drug Surveillance Program.[9] This program monitors all drug exposures in several hospitals, with information being extracted from clinical records and by interviews with patients and physicians. Of over 11,000 hospitalised medical patients who had opioids administered during their hospital stay, only four were reported to have become addicted.

Abnormal drug-seeking behaviour was not seen when long-term opioids were used for postherpetic neuralgia, [10] phantom limb pain,[11] chronic spinal pain, [12] and pain of mixed but well defined origin. [13] Taub described 313 personally treated patients with intractable pain who were maintained on opioid analgesics for up to 6 years. Only 13 patients presented serious management problems, and each of them had a history of substance abuse (opioids or alcohol).[14] Portenoy also identified this risk factor in his study of 38 patients treated with opioids for non-malignant pain; the two patients who required escalating doses of opioids each had a history of drug abuse.[15]

At the other end of the spectrum, Maruta found that 65 per cent of 144 consecutive patients referred for chronic non-malignant pain management were abusing or 'dependent on' weak and strong opioid drugs and had a strong family history of alcohol abuse.[16] These data seem contradictory, however many factors, including basic definitions of dependence, have been a problem in such studies to date.

Addiction has been shown to be more complex than just the result of repeated exposure to a drug. There was high prevalence of opioid addiction among US soldiers in Vietnam; however, surveys of returning veterans demonstrated that a large proportion of those who abused heroin stopped this activity abruptly on return to a normal life in the U.S. and that the relapse rate was low. [17] In sharp

contrast, a group of drug addicts who underwent a 6 month in-patient treatment programme under the Narcotic Addict Rehabilitation Act were re-addicted within 6 months of their release.

These observational studies and case series give an indication of a spectrum of response to opioid analgesia, ranging from appropriate use to inappropriate drug-seeking behaviour.

However, misapprehension fuelled by limited good quality data continues to fuel underprescription of opioids. A recent analysis of publications pertaining to drug or alcohol dependence in chronic pain patients found less than one-tenth of these publications used acceptable criteria for drug misuse or even gave percentages of dependence problems. Physician opiophobia is an area of medicine which needs to be addressed, however a fundamental requirement is the need for meaningful, good quality data.[18]

Addiction has been defined as 'a behavioural pattern of drug use, characterised by overwhelming involvement with the use of a drug (compulsive use), the securing of its supply, and the high tendency to relapse after withdrawal'.[19] A task force of the Panels on Alcoholism and Drug Abuse of the American Medical Association (AMA) Council on Scientific Affairs formulated the following definitions:

Addiction: 'a chronic disorder characterised by the compulsive use of a substance resulting in physical, psychological or social harm to the user and continued use despite that harm.'[20]

Addict : ' a person who is physically dependent on one or more psychoactive substances, whose long-term use has produced tolerance, who has lost control over his intake, and would manifest withdrawal phenomenon if discontinuance were to occur.' Although this includes the terms physical dependence and tolerance, these exist along with loss of personal control in the addict. In the patient with pain, physical dependence and tolerance may occur but without loss of personal control.

It is obvious that these definitions of addiction or psychological dependence have limited value in the patient with either chronic malignant or chronic non-malignant pain and a more exploratory approach

is required to extract any evidence of psychological dependence in these groups. It is entirely reasonable that if opioids control pain for our patients they then will continue to request them. In addition, if inappropriate dosing is prescribed, the patient will reasonably request an increase in dose to control pain. This sensible therapeutic use is obviously not addiction.

We 'know' that addiction generally is not a problem in patients receiving opioids for pain. However, we do not know why, and we are unable to explain it on the basis of existing data. This observational study was planned with the intention of making a preliminary attempt to characterise, compare and contrast three groups of patients, to see whether there were any essential demographic differences, psychological differences and differences in the way the drugs were used. The three groups were: patients with cancer pain, patients with chronic non-malignant pain and drug addicts on a methadone maintenance programme.

The hypothesis for this study is: patients with pain and using opioid analgesia do not show patterns of opioid use similar to drug addicts.

Aim

To begin to investigate the question of addiction to opioids in patients with pain we studied three groups: cancer patients taking opioids for pain, patients with chronic non-malignant pain taking regular opioids and drug addicts on a methadone maintenance programme. Medical and personal data, mood, and patterns of drug use were compared in the three groups. In addition patients were rated using validated scales for opioid addiction (S.D.S) [21] and for opioid withdrawal (S.O.W.S) [22]

Methods

Ethical approval for the study was obtained from St Thomas' Hospital and all included gave written informed consent. Thirty patients in each of the 3 patient groups were enrolled in the study. Consecutive patients with cancer pain on strong opioids and a prognosis of at least 3 months referred to

the palliative care team of a large London teaching hospital with an oncology unit were considered for inclusion in the study. All patients approached agreed to take part in the study. Many of these patients referred to the palliative care team for pain control, had difficult pain syndromes and were using large quantities of opioids. The oral morphine equivalent doses in this study group were unusually high, at the upper end of the usual range, however some of the patients in this study had severe neuropathic pain, shown to require very high opioid doses.

The patients with chronic non-malignant pain included in the study had been referred to a tertiary Chronic Pain Management Unit in the same teaching hospital. Consecutive patients referred on strong opioids were approached to take part in the study and all agreed. Referrals to the unit came from all over the UK, and from general practice as well as from hospital-based specialties.

The drug addicts included in the study were taken from consecutive cases attending a methadone maintenance programme in a major London teaching hospital, serving a local South London population. All drug addicts approached to take part in the study agreed. Drug addicts on a methadone maintenance programme will clearly continue to use illicit drugs in addition to the prescribed methadone.

The following information (see appendices 1-4) was collected:

1. Demographic data and drug use: at entry to the study

   - basic medical and personal information
   - past psychiatric history
   - drug regimen
   - use of unprescribed drugs
   - HAD score[23] (repeated monthly), this has 7 anxiety and 7 depression questions

2. Assessments

i) Initial questions at entry:

- reasons for taking opioids, using visual analogue scales (V.A.S.) e.g. to relieve pain, to calm, to help sleep, to feel good . . .
- fears about opioids - free text
- prompts to take next dose based on opioid withdrawal symptoms scale (S.O.W.S) in addition to questions relating to pain and breathlessness (Yes or No answers)
- maximum daily opioid dose in past week
- pain severity; now and average over past week (V.A.S.)
- pain distress; now and average over past week (V.A.S.)
- opioid side-effects (V.A.S) (drowsiness, constipation, nausea, vomiting)
- disturbed sleep (V.A.S.)

ii) Daily diary (for the first week only, completed in evening and refers to that day)

- pain severity (V.A.S.)
- pain distress (V.A.S.)
- opioid side-effects (V.A.S)
- general well-being (V.A.S)
- Regular opioid dose
- extra opioid used
- effect of medication (V.A.S) - regular and extra
- other drugs used
- questions relating to anxiety and emotions

iii) Weekly diary (for up to 2 years in cancer patients, however for first month only in other groups):

- maximum dose of opioid taken in 24 hour period over this week
- questions as per daily diary

iv) Follow-up questions (monthly for 3 months and up to 2 years in some cancer patients)

- preoccupation with opioids (V.A.S.)
- effect of opioids on mood (V.A.S.)
- questions from Severity of Dependence Scale (S.D.S.)
- prompts for taking next dose; S.O.W.S. questions in addition to pain and breathlessness questions (Yes/No replies)
- desires regarding opioid dose changes
- reasons for using opioids (V.A.S.)

The Short Opioid Withdrawal Scale (S.O.W.S) is in the appendices (no.1) and the Severity of Dependence Scale (S.D.S) appendix 2. This S.D.S. focuses on control over opioid dose and difficulty stopping or interrupting use. These were clearly developed for use in a drug addiction population, however, in the absence of a scale validated for use in patients initially prescribed opioids for analgesia, these have been used in this study.

These data were collected over the following

1. initially at entry into the study
2. daily for 1 week - (questions relating to drug doses, effectiveness, reasons for taking dose, side-effects)
3. weekly for 4 weeks
4. monthly for 3 months

The questionnaires were completed by the cancer pain patients at out-patient follow-up appointments (the daily diary was completed in between). They were mostly out-patients.

The chronic pain patients were recruited to the study between initial interview on referral and the start of treatment several months later. This group completed the initial questionnaire at referral and returned the remainder by pre-paid post.

The drug addicts completed the initial questionnaires at the methadone maintenance clinic and the remainder during the attendance at the day unit.

Statistical analysis

All opioids were converted to morphine equivalent 24 hour doses using accepted equianalgesic conversions. From the daily diary data, means for 24 hour opioid doses, dose efficacy, pain intensity, and pain distress were calculated. For each patient group, correlations were calculated between mean daily dose, mean dose efficacy, mean pain severity, maximum pain severity, mean pain distress, maximum pain distress, HAD anxiety score, HAD depression score, and age, using Pearson's correlations for parametric data and Spearman's rank correlations for rating scale and HAD data. The number of extra opioid doses over the week of the daily diary was obtained, and compared by correlation with mean and maximum pain severity and pain distress. The daily opioid dose was compared with ratings of symptoms of constipation, nausea and vomiting, sleep disturbance, drowsiness, general wellbeing, and pain severity and pain distress by correlation.

The number of patients in each group endorsing each of the listed opioid withdrawal symptoms which cued opioid use was grouped using the categories of (1) attributable to withdrawal (craving, sneezing, running nose, yawning, sweating, stomach cramps), (2) emotional (irritability, anxiety, restlessness), and (3) somatic excluding pain (stiffness, shaking, feeling hot or cold, heart pounding, breathlessness). Comparison of individual symptoms and of these three categories was made using χ^2 or Fisher's exact test where cell numbers were small.

Mean severity of dependence SDS scores were computed from the monthly data and since they were reasonably normally distributed, those of the cancer patients and chronic pain patients compared using t-tests.

All analyses were carried out using SPSS 6.01 for Windows.

The disc at the back of this thesis contains all the data for the addiction and tolerance studies using SPSS 6.01 for windows.

Results

Fourteen cancer patients, 27 chronic non-malignant pain patients and 30 drug abusers completed data. They had been using opioids for a mean of 6 months, 2.2 years and 13 years respectively, in median daily oral morphine equivalent doses of 1320 mg, 700 mg and 160 mg. Cancer and chronic pain patients had mean age of 59 years and 43 years, drug abusers were younger with a mean age of 34 years.

Size of dose

For cancer patients, the mean daily dose was unrelated to mean pain intensity or distress ($r = 0.220$ and $r=0.201$, $p>0.5$), or to mean dose efficacy scores, V.A.S. for dose efficacy ($r=0.109$, $p>0.5$). Nor was it related to age ($r=0.318$, $p>0.1$), or to HAD anxiety or depression scores ($r=0.229$, $r=0.368$, both $p>0.1$).

For chronic pain patients, higher mean daily doses were not associated with mean pain severity and distress ($r=0.106$, $r=0.273$), with mean dose efficacy ($r=0.292$), nor with anxiety and depression scores ($r=0.000$, $r=0.241$), nor age ($r=0.172$).

For methadone maintenance patients, pain questions were irrelevant to their use, but a higher mean daily dose was associated with a greater depression score ($r=0.601$ $p<0.005$) but not anxiety ($r=0.032$) or with age ($r=0.230$).

Mean dose efficacy:

For cancer patients, mean dose efficacy was inversely related to mean ratings of pain severity, ($r=0.762$, $p< 0.025$) and distress, ($r=0.767$, $p < 0.025$), but not to maximum pain severity and distress, ($r=0.045$, $r=0.533$). In chronic pain patients, mean dose efficacy was unrelated to mean or maximum pain severity ($r=0.192$, $r=0.088$) or pain distress ($r=0.034$, $r=0.053$). No relationships could be found between mean or maximum ratings of dose efficacy and any other variable for drug users.

Cues to take a dose of opioid:

Table I illustrates the questions asked about reason for taking the next dose of opioid. These questions include the short opiate withdrawal scale questions, in addition to some questions related to pain and breathlessness, the therapeutic indications for opioids. These prompts were analysed by grouping them into withdrawal symptoms (i.e. symptoms highly unlikely to be due to cancer or pain in these groups) emotional variables or somatic variables. While some emotional and somatic variables are included in the short opiate withdrawal scale, this scale was not designed for pain patients and no useful analysis was obtained using the complete score in all 3 groups.

There is a significant difference between the pain groups and the drug addicts ($x^2 = 30$, $p < 0.0001$) when symptoms only attributable to withdrawal e.g. craving, sneezing, running nose, are examined as prompts to take a dose of opioid. Similarly for emotional variables (anxiety and/or feeling irritable and/or feeling restless), there is a significant difference between pain patients and drug addicts ($x^2 = 13.2$, $p < 0.005$)

Table 1

Prompts to take dose

	Cancer	Chronic Pain	Meth Maint	X^2	P
N	11	27	21		
by clock	11	15	12	7.5	<0.05
pain severity	10	26	4	35.6	<0.0001
pain distress	9	20	6	12.9	<0.005
problems sleeping	2	14	12	4.7	
anxiety	1	3	12	14.9	<0.001
feeling restless	0	3	12	17.8	<0.0005
feeling irritable	1	3	11	12.5	<0.005
stiffness	2	8	8	1.4	
breathlessness	2	1	2	2.2	
stomach cramps	1	2	13	21.4	<0.0001
heart pounding	0	2	3	1.7	
craving	0	1	16	33.4	<0.0001
shaking/twitching	0	4	10	9.9	<0.01
feeling hot and cold	0	1	16	35.7	<0.0001
running nose/eyes	0	1	14	29.3	<0.0001
sneezing	0	0	11	24.1	<0.0001
yawning	0	0	15	24.1	<0.0001

Analysis of the somatic variables excluding pain, (stiffness and/or shaking and/or breathlessness and/or feeling hot and cold and/or heart pounding), once again shows a difference between pain patients and drug addicts ($x^2 = 12.5$, $p < 0.005$).

For cancer patients, almost all took their opioids by the clock i.e. regularly, as prescribed and there was no relationship between the tendency also to take according to pain with emotional or other symptom cues. The best therapeutic outcome in cancer pain comes from regular opioid use and this is how opioids were prescribed for this group. In addition to regular doses prescribed for cancer pain, extra opioid can be taken as required for 'breakthrough' or uncontrolled pain. The size of this dose is calculated for each patient.

For chronic pain patients there was a very strong association between taking according to emotional cues (anxiety and irritability) and taking according to other somatic symptoms (Fisher's exact test p=0.012). Opioid drugs are often taken irregularly in chronic non-malignant pain patients. This is expected since an irregular pattern of drug use is the usual before entering the pain management programme.

For drug users, there was no relationship between taking opioids and emotional cues, or according to other somatic symptoms (other than those classified as 'withdrawal' symptoms).

Figures I to X (p29-31) illustrate these findings: red represents cancer patients, green, chronic non-malignant pain patients and blue, drug addicts.

Taking extra doses of opioid:

For cancer patients, the number of extra opioid doses taken over the week was associated weakly with mean pain severity ($r=0.647$, $p<0.05$) and distress ($r=0.697$, $p<0.05$), and more strongly with maximum pain severity ($r=0.855$, $p<0.005$) and weakly with maximum pain distress ($r=0.678$, $p<0.05$).

For chronic pain patients, the number of extra opioid doses was associated with no pain variables ($r=0.125$ to $r=0.316$) for the whole group, but for those scoring below the cutoff point of 11 on the HAD depression scale, that is, whose scores were not of clinical concern, there was a very similar pattern to that seen in the cancer patients between the number of extra opioid doses over the week and pain scores: with mean pain severity ($r=0.596$, $p<0.05$), with maximum pain severity ($r=0.774$, $p<0.001$), and with maximum pain distress ($r=0.581$, $p<0.05$).

For drug users, there was no predictor of using any drugs in addition to the methadone script. Drug availability is the crucial factor in the addict group.

For none of the three groups was taking extra opioid doses over the week associated with anxiety or depression, (HAD scale) or taking versus not taking extra opioid doses with initial fears (that is, at the start of taking opioids) about possible addiction or about other issues such as adverse effects.

Symptoms of dependence score: (Appendix II)

The S.D.S. was completed monthly. Good quality S.D.S. data were only obtained from 5 patients with cancer pain and 15 chronic non-malignant pain patients. Mean S.D.S. scores were similar across the two groups (10.3 (s.d. 2.5), 9.5 (s.d. 2.1) respectively), for both this is a clinically significant score from a possible maximum of 15. However, both groups of pain patients scored high on having difficulty with the idea of stopping and lower on anxiety and worry about opioid use. There was no relationship between these concerns about opioid use and mean daily oral morphine equivalent dose.

Relationship between oral morphine equivalent dose and symptoms:

There was no linear relationship between oral morphine equivalent dose and mean daily scores over the first week of constipation, nausea and vomiting, sleep disturbance, general well-being, drowsiness, pain severity or pain distress. Even if the highest opioid doses are excluded along with those rating mean constipation less than 1 on a V.A.S. (0-10), there is no relationship between opioid dose and constipation.

Chronic non-malignant pain patients were more likely to vary opioid dose; seventy per cent, compared to 30% of cancer patients and 19% of drug addicts.

Discussion

In the cancer pain group the size of opioid dose was unrelated to pain severity or distress. The size of opioid dose used to control cancer pain is likely to relate to a number of variables relating to the individual and the pain syndrome. We know some pains, particularly neuropathic pains require larger opioid doses.[24] These results are

consistent with the neuropharmacology and neurophysiology of cancer pain and where opioids are used regularly as in this patient group.

The chronic pain patients also showed no relationship between opioid dose and pain severity or distress. Once again this is expected for the same reasons as mentioned for cancer pain.

With the methadone maintenance group in this study, higher doses of illicit drugs are associated with higher depression scores.

The opioid dose efficacy results reflect the beneficial pattern of regular opioid regimens in cancer patients and the more chaotic and at times less effective regimens in chronic pain patients. However there was no evidence of analgesic tolerance in either pain group. Opioids remained effective if used regularly.

Clearly in drug users the efficacy of drug use will depend on individual factors, e.g. degree of tolerance. There was no predictor of opioid use in drug addicts which is most likely due to the fact that drug availability is the overwhelming keystone to opioid use in this group.

The pain patients were understandably not keen on stopping opioid use because of the beneficial effects on pain: this is an example of how a score developed for drug addicts is not helpful in other populations.

Conclusions

Cancer pain and chronic non-malignant pain patients used opioids mainly to relieve pain; drug abusers used opioids for mood and sleep.

Chronic pain patients were more depressed than both other groups and took extra doses when pain was more distressing; cancer patients took extra opioids when pain was poorly controlled; for drug abusers there was no obvious cue for drug use and availability seems the most likely factor.

These analyses show no evidence of opioid dependence or opioid withdrawal symptoms in the 2 pain groups (if somatic symptoms are excluded), using these scales validated for use in drug addicts. However, more useful and meaningful data has been obtained by analysis of opioid use, effectiveness of opioids, reasons for use, methods of use.

Opioids have predictable pharmacokinetic and pharmacodynamic profiles and are therefore prescribed in a regular fashion for chronic cancer pain with the aim of pain control while accepting that at times extra doses will be required for 'breakthrough' pain. This strategy works for the majority (80%) of cancer patients.[25] It is obvious from this data that although some of the cancer patients in this study had difficult pain, requiring very large doses of opioids, all of the cancer pain group used opioids to relieve pain and took extra doses when the pain was poorly controlled. The efficacy was predictably related to lower levels of pain severity.

Chronic pain patients traditionally use analgesics in a less structured way than cancer pain patients and this is commonly prescriber dictated. Chronic pain management with opioids is poorly addressed in the U.K. However, it is interesting to note that higher doses coexisted with better pain control and a regular regimen was associated with higher drug efficacy. Chronic pain patients otherwise used opioids in response to emotional cues such as irritability and anxiety. It is common to find these features with uncontrolled chronic pain and they are often misinterpreted in clinical practice. This group tended to use extra doses with higher pain severity and pain distress ratings. This is another sign of appropriate opioid use in chronic pain.

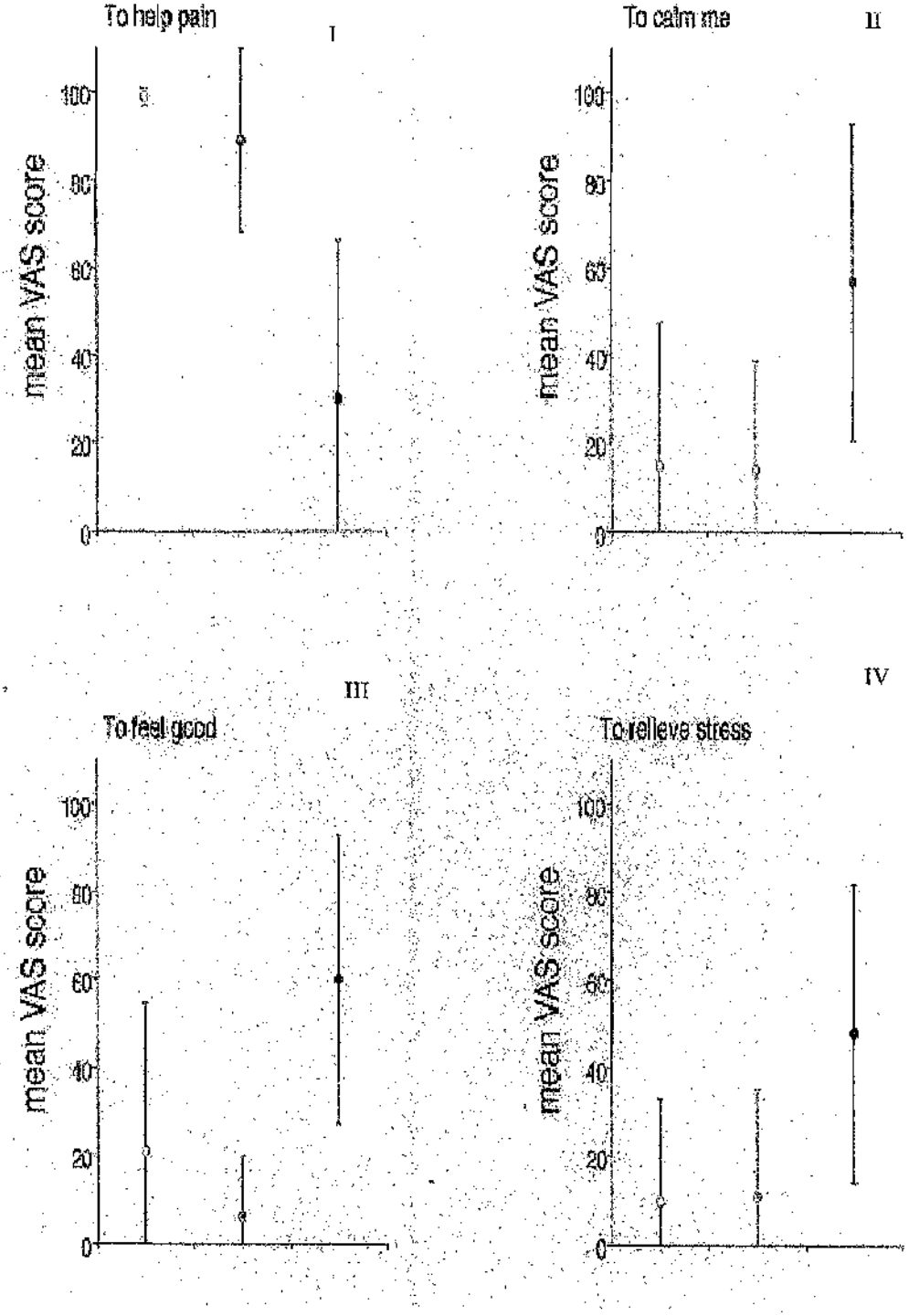
The drug addict group on higher doses of illicit drugs had more depression and lower maximum rating of efficacy, the latter a sign of pharmacological tolerance. This was not evident in the pain groups. There was no predictor at all of when drug addicts would use illicit drugs and the assumption must be that unlike the pain groups this is related to availability.

There are profound differences in use and subjective effects of opioids between pain patients and drug abusers. This study goes beyond the inadequate definition of addiction which has been unhelpful by itself in the chronic pain situation. The situation of addiction or psychological dependence in the pain situation may be further clarified by examination of patients on a regular opioid regimen and good pain control over a longer time. This is addressed in the next chapter. The chronic drug-seeking behaviour of chronic pain patients who get analgesia from opioids is often misinterpreted. This is 'pseudo-addiction'.

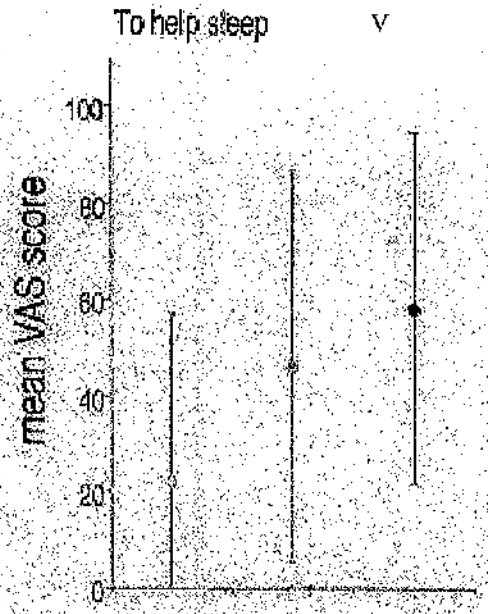
The paradoxical position of opioids, and a sensible, acceptable approach to their use could be clarified by communication between addiction specialists and physicians managing pain. The former have used their observations in addicts to establish a language and understanding of risk factors and outcomes of abuse, but have little if any experience of opioid use for pain, the latter have insufficient knowledge of the criteria by which drug abuse is defined and strategies of management of abuse.

Pain relief is a fundamental duty of every physician, however, proactive communication between medical disciplines about the use of opioids is lacking.

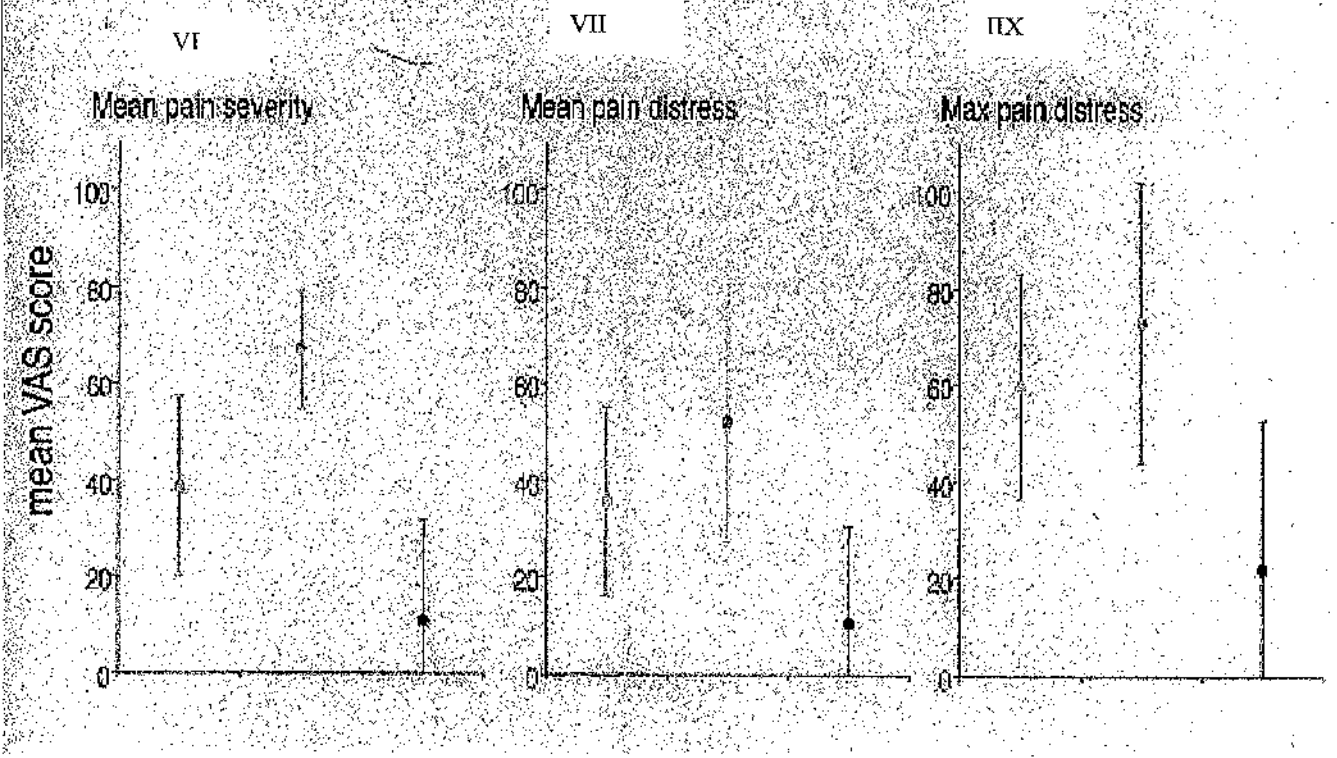
The following reasons for taking opioids showed statistically significant Differences between 1) Cancer (red) and Chronic pain (green) patients And 2) Drug abusers (blue):



The following was statistically significant between only cancer patients and drug abusers:



Opioid doses showed statistically significant differences between 1) cancer and chronic pain patients and 2) drug abusers:



The following significant difference between cancer patients(red) and drug abusers (blue):

Fig IX

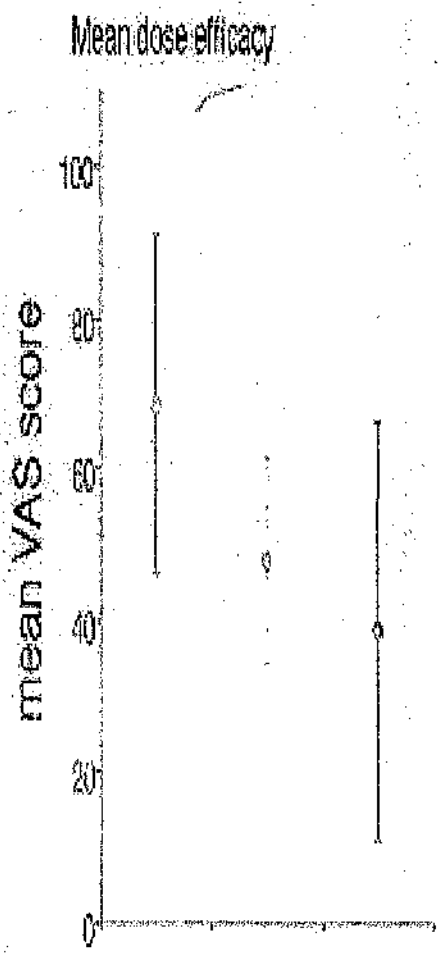
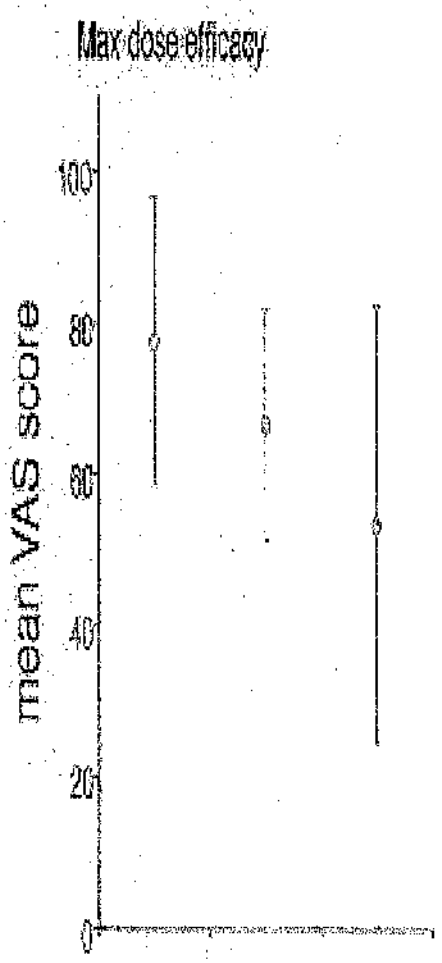


Fig X



Initial Questions

Patient Name .....

Patient No .....

Today's Date ...../...../.....

INITIAL QUESTIONNAIRE (+ demographic data + HAD: supervised completion

1. Opioids have a range of effects. Please indicate on the lines below what effects they have when you take them. You can put a mark anywhere along the line, between the left hand end, 'not at all', and the right hand end, 'very much so'.

I take opioids to help relieve pain

not at all very much so

I take opioids to help calm me

not at all very much so

I take opioids because I feel worse if I don't

not at all very much so

I take

DAILY DIARY

Patient Name .....

Patient No .....

Today's Date ...../...../.....

DAILY DIARY (daily first week, self-completion)

1. If you are in pain:
   On average how severe was your pain today?

No pain _____ worst pain possible

On average how much did your pain distress you today?

No distress _____ worst distress possible

2. How much have you been feeling sick (nauseous) today?

Not at all _____ all the time

3. Have you been constipated today?

Not at all _____ severely

4. Has your sleep been disturbed today?

Not at all _____ very disturbed

5. Have you felt drowsy today?

Not at all drowsy _____ extremely drowsy

6. How has your appetite been today?

Very poor appetite _____ very good appetite

7 How have you been feeling generally today?

Very unwell _____ very well

Regular medication/prescribed medication

8. Total dose today .....mg

9. How much effect did you get from your regular medication today? Please mark the line at the point which best represents the relief you get from your regular medication.

No effect _____ Maximum effect

Extra Medication

10. Did you take any other opioid today? Yes No

If yes:

What did you take? .....

What dose did you take?.....mg

How often did you take it? .....times per day

How much effect did you get from this?

No effect _____ Maximum effect

11. Did you take any other drug today? Yes No
(other than your regular prescribed drugs)

If yes:

What did you take? .....

What dose did you take? .....mg

How often did you take it? .....times per day

12. Did you get any unpleasant side effects from either your regular /prescribed medication or the extra medication/ (please ring) Yes No

If yes, please list the side effects .....

.....

13. Did anything else affect how much opioid you took today? (please ring) Yes No

If yes, please say briefly what affected how much you took .....

14. Did anything else affect how you felt today? (please ring) Yes No

If yes, please say briefly what it was, and how you felt .....

.....

15. If you are in pain, do you drink alcohol to relieve the pain?

(Please ring) Yes No

If yes, how often do you do so? .....times a day

If yes, how much do you drink? .....in total each day

DAILY DIARY

Patient Name .....

Patient No .....

Today's Date ...../...../.....

DAILY DIARY (daily first week, self-completion)

1. If you are in pain:
   On average how severe was your pain today?

No pain _____ worst pain possible

On average how much did your pain distress you today?

No distress _____ worst distress possible

2. How much have you been feeling sick (nauseous) today?

Not at all _____ all the time

3. Have you been constipated today?

Not at all _____ severely

4. Has your sleep been disturbed today?

Not at all _____ very disturbed

5. Have you felt drowsy today?

Not at all drowsy _____ extremely drowsy

6. How has your appetite been today?

Very poor appetite _____ very good appetite

7 How have you been feeling generally today?

Very unwell _____ very well

Regular medication/prescribed medication

8. Total dose today .....mg

9. How much effect did you get from your regular medication today? Please mark the line at the point which best represents the relief you get from your regular medication.

No effect _____ Maximum effect

Extra Medication

10. Did you take any other opioid today? Yes No

If yes:

What did you take? .....

What dose did you take?.....mg

How often did you take it? .....times per day

How much effect did you get from this?

No effect _____ Maximum effect

11. Did you take any other drug today? Yes No
(other than your regular prescribed drugs)

If yes:

What did you take? .....

What dose did you take? .....mg

How often did you take it? .....times per day

12. Did you get any unpleasant side effects from either your regular /prescribed medication or the extra medication/ (please ring) Yes No

If yes, please list the side effects .....

.....

13. Did anything else affect how much opioid you took today? (please ring) Yes No

If yes, please say briefly what affected how much you took .....

14. Did anything else affect how you felt today? (please ring) Yes No

If yes, please say briefly what it was, and how you felt .....

.....

15. If you are in pain, do you drink alcohol to relieve the pain?

(Please ring) Yes No

If yes, how often do you do so? .....times a day

If yes, how much do you drink? .....in total each day

Weekly Diary

Patient Name .....

Patient No .....

Today's Date ...../...../.....

WEEKLY DIARY (weekly throughout the study, self-completion)

1. What is the maximum daily dose this week of your opioid medication ..... mg

   Have you made any changes to your opioid medication/opioid use this week?
   If so what changes?

   .....

   .....

2. If you have pain, how severe has your pain been today?

No pain possible _____ worst pain possible

3. On average, how severe has your pain been this week?

No pain possible _____ worst pain possible

4. If you have pain, how much has it distressed you today?

No distress _____ worst distress possible

5. On average, how much has your pain distressed you this week?

No distress _____ worst distress possible

6. How much have you been feeling sick (nauseous) this week?

Not at all _____ all the time

7. Have you been constipated this week?

Not at all _____ very severely

8. Has your sleep been disturbed this week?

Not at all _____ very disturbed

9. Have you felt drowsy during the day this week?

Not at all drowsy _____ extremely drowsy

10. How has your appetite been this week?

Very poor appetite _____ very good appetite

11. How have you been feeling generally this week?

Very unwell _____ very well

Regular medication/prescribed medication

12. Total dose today .....mg

13. How much effect did you get from your regular medication today? Please mark the line at the point which best represents the relief you get from your regular medication.

No effect _____ maximum effect

Extra medication

14 Did you take any other opioid today? Yes No

If yes:

What did you take? .....

What dose did you take?.....mg

How often did you take it? .....times per day

How much effect did you get from this?

No effect _____ Maximum effect

15 Did you take any other drug today? Yes No

(Other than your regular prescribed drugs)

If yes:

What did you take?.....

What dose did you take .....mg

How often did you take it?.....times per day

16 Did you get any unpleasant side effects from either your regular/prescribed medication or the extra medication? (please ring) Yes No

If yes, please list the side effects .....

.....

17 Did anything else affect how much opioid you took today? (please ring) Yes No

If yes, please say briefly what it was, and how you felt

.....

.....

18 Did anything else affect how you felt today/ (please ring) Yes No

If yes, please say briefly what it was, and how you felt

.....

.....

19 If you are in pain, do you drink alcohol to relieve the pain?

(please ring) Yes No

If yes, how often do you do so? .....times a day

If yes, how much do you drink? .....in total each day

Follow-up Questions

Patient Name .....

Patient No .....

Today's Date ...../...../.....

FOLLOW-UP QUESTIONNAIRE (monthly at clinic visit or self-completion)

Please think of your opioid use during the last week when you answer these questions.

1. How much do you think about your opioids during the day?

never _____ all the time

2. How much do you think the opioids affect your mood?

negative effect on mood _____ positive effect on mood

Please answer each question by circling one response only.

Over the last week . . .

3. Did you think that your opioid use was out of control?

Never or almost never	Sometimes	Often	Always or nearly always

4. Did the prospect of missing a dose make you very anxious or worried?

Never or almost never	Sometimes	Often	Always or nearly always

5. Did you worry about your opioid use?

Never or almost never	Sometimes	Often	Always or nearly always

6. Did you wish you could stop?

Never or almost never	Sometimes	Often	Always or nearly always

7. How difficult would you find it to stop using opioids or to go without opioids?

Impossible	Very difficult	Quite difficult	Not Difficult

8. **How do you decide when to take your next dose?** Please answer Yes or No to as many reasons as apply to you.

By the clock	Yes	No
Pain intensity - when pain is severe	Yes	No
Pain distress - when pain distresses you	Yes	No
Aches in muscles	Yes	No
Breathlessness	Yes	No
Feeling anxious	Yes	No
Feeling restless	Yes	No
Feeling irritable	Yes	No
Feeling sick	Yes	No
Difficulty sleeping	Yes	No
Feeling stiff	Yes	No
Heart pounding	Yes	No
Feeling hot and cold	Yes	No
Had gooseflesh	Yes	No
Stomach cramps	Yes	No
Runny eyes or nose	Yes	No
Feel craving	Yes	No
Yawning	Yes	No
Sneezing	Yes	No
Sweating	Yes	No
Twitching/shaking	Yes	No

9. **Would you like to change your regular dose of opioid?** (please ring one)

increase decrease no change

How would this improve things?

.....

.....

10. **Opioids have a range of effects. Please indicate on the lines below what effects they have when you take them. You can put a mark anywhere along the line, between the left hand end, 'not at all', and the right hand end, 'very much so'.**

I take opioids to help relieve pain

not at all _____ very much so

I take opioids to help calm me

not at all _____ very much so

I take opioids because I feel worse if I don't

not at all _____ very much so

I take opioids to help my sleep

not at all _____ very much so

I take opioids to make me feel good

not at all _____ very much so

I take opioids to help my breathlessness

not at all _____ very much so

I take opioids to relieve stress

not at all _____ very much so

S.O.W.S

Appendix I

Name:	**Date:**

Please put a tick in the appropriate box if you have had any of the following during the last 24 hours.

	None	Mild	Moderate	Severe
Feeling sick				
Stomach cramps				
Muscle spasms/twitching				
Feelings of coldness				
Heart pounding				
Muscular tension				
Aches and pains				
Yawning				
Runny eyes				
Insomnia/ problems sleeping				

S.D.S

Appendix II

3. Did you think that your opioid use was out of control?

Never or almost never	Sometimes	Often	Always or nearly always

4. Did the prospect of missing a dose make you very anxious or worried?

Never or almost never	Sometimes	Often	Always or nearly always

5. Did you worry about your opioid use?

Never or almost never	Sometimes	Often	Always or nearly always

6. Did you wish you could stop?

Never or almost never	Sometimes	Often	Always or nearly always

7. How difficult would you find it to stop using opioids or to go without opioids?

Impossible	Very difficult	Quite difficult	Not Difficult

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Chapter 4

Note to examiner: methods section is the same as chapter 2.

Clinical Tolerance to Opioids

Clinical tolerance to opioid analgesia in man results from a complex series of phenomena. Tolerance refers to a phenomenon in which exposure to a drug results in the diminution of an effect or the need for a higher dose to maintain an effect.[1] In quantitative terms tolerance is demonstrated by a shift to the right of the dose-response curve and an increase in the opioid ED50 value (the dose required to produce an effect in 50% of the population).[2, 3]

Tolerance can be innate i.e. genetically determined, or acquired. Acquired tolerance can be pharmacokinetic, pharmacodynamic or learned tolerance.

Pharmacokinetic tolerance refers to changes in the distribution or metabolism of the drug after repeated drug administrations that result in reduced concentrations in the blood and subsequently at the sites of drug action. The most common mechanism is an increase in rate of metabolism of the drug, as in the case of barbiturates.

Pharmacodynamic tolerance refers to adaptive changes that have taken place within systems affected by the drug, such as drug-induced changes in receptor density and second-messenger systems, so that response to a given concentration of the drug is reduced.[3]

Learned tolerance refers to a reduction in the effects of a drug as a result of compensatory mechanisms that are learned. Conditioned tolerance is a type of learned tolerance. It is situation specific and develops when environmental cues are consistently paired with the administration of the drug.[4]

When a drug affects homeostatic balance by producing sedation and changes in blood pressure, heart rate and gut motility, there is usually a reflex counteraction or adaptation that attempts to restore the status quo. If the drug is always preceded by the same cues, the adaptive response to the drug will be

learned and this will prevent the full manifestation of the drugs effect (tolerance). If the drug is taken under different circumstances e.g. after a different ritual in the case of the drug addict, tolerance to that particular dose is reduced and the drug effect enhanced. This explains why a drug addict may suffer a respiratory arrest with a dose of opioid, which had previously resulted in no respiratory depression, if the drug is taken under different circumstances. This is a generally accepted phenomenon in A & E departments.

It is claimed that patients with pain who receive opioids repeatedly, develop tolerance to the analgesic effects.[5] Opioid tolerance is manifest when a given dose of an opioid produces a decreased effect or when a larger dose is required to maintain the original effect. This tolerance is not due to pharmacokinetic changes in the disposition of the opioid but rather it is a pharmacodynamic type of tolerance that results from neuroadaptive processes.

The loss of analgesic efficacy as a result of tolerance does not usually limit the clinical use of opioid drugs, because the development of tolerance to the respiratory depressant and other limiting effects allows the dose of opioid to be increased through dose titration.

The usual method of assessing the presence or absence of tolerance in the clinical setting is dose escalation. Studies using opioid dose escalation show that the rate and extent of tolerance differ dramatically among pain patients.[6, 7] Unfortunately the yardstick of disease progression causing opioid dose escalation can be a very inaccurate measurement. Disease progression leading to an increase in pain is not always easily measured even with sensitive investigations. Furthermore, a stable opioid dose does not necessarily imply no analgesic tolerance, since pains may resolve either spontaneously or with some intervention e.g. radiotherapy or chemotherapy. It is reasonable to say that opioid dose escalation is the response to a number of variables which leave the patient with an increase in the subjective sensation of pain. In the situation of uncontrolled pain, the efficacy of an opioid dose at any given time is an indication of lack of pharmacological tolerance to the analgesic effect of the opioid dose which the individual takes at that time. The patient and his pain are their own controls in this situation, assuming no significant change in background pain. Similarly pharmacological tolerance to

the hedonistic effects of opioids in drug abusers can be measured at any given time point by asking about the hedonistic or euphorigenic effectiveness of a dose.

The side-effects of opioids in the chronic dosing situation are sedation, dry mouth, constipation and nausea and vomiting. These are usually described as initiation effects and are said to be associated with subsequent dose increases. Tolerance develops at different rates to each of the opioid effects. The measurement of tolerance to wanted effects i.e. analgesia as compared to tolerance to unwanted effects has not been measured with any precision in man. Interestingly, the analogy in drug addicts, tolerance to hedonistic effects as compared to tolerance to respiratory depression, constipation, nausea and vomiting has also not been measured.

Despite the limitations of just looking at pain stimulus there have been useful studies of patterns of opioid use in patients with pain. They demonstrate that changes in the pain stimulus, usually progression of the tumour in cancer pain patients, is the most common cause of opioid dose escalation.[7] In addition, with chronic non-malignant pain, stable doses of opioids can provide relief for years.[8] While clinical studies of opioid use in patients with cancer pain do not raise anxiety over the issue of analgesic tolerance, the phenomenon of morphine tolerance in central hypersensitivity states is discussed in Chapter 10.

Our study comparing 3 groups using opioids, provides interesting insight into clinical tolerance as well as addiction. This was examined by asking critical questions around tolerance. The three groups were: patients with cancer pain, patients with chronic non-malignant pain and drug abusers on a methadone maintenance programme. Medical and personal data, mood and patterns of drug use were compared in the 3 groups.

Aim:

The aim of this part of the study was to establish the relationship of opioid dose to analgesic response in pain patients and opioid dose to hedonistic effects in drug abusers and also to compare opioid dose to unwanted opioid effects: sedation, nausea, vomiting, and constipation, in all 3 groups. In addition, the pattern of dose, efficacy of dose, pain and side-effects was followed over time; 3 months for chronic non-malignant pain and up to 2 years for patients with cancer pain.

The issue of rate of opioid dose escalation is complex in the pain situation, however, examination of the above parameters was expected to give information about patterns of opioid dosage and help in some way to evaluate more objectively clinical tolerance. Similarly in the drug addicts on the methadone maintenance programme rate of escalation is complicated due to both availability and reporting. We know that to achieve the same hedonistic effects over time, drug addicts do have to increase their dose.

Methods

Ethical approval for the study was obtained from St Thomas' Hospital and all included gave written informed consent. Thirty patients in each of the 3 patient groups were enrolled in the study. Consecutive patients with cancer pain on strong opioids and a prognosis of at least 3 months referred to the palliative care team of a large London teaching hospital with an oncology unit, were considered for inclusion in the study. Many of these patients by definition had difficult pain syndromes and were using large quantities of opioids. The oral morphine equivalent doses in this study group were unusually high at the upper end of the distribution and reflected difficult pain treated for years with opioids. All patients approached agreed to take part in the study. This was therefore an ideal group in whom to study pharmacological tolerance.

The patients with chronic non-malignant pain included in the study were referred to a tertiary Chronic Pain Management unit in the same teaching hospital. Consecutive patients referred on strong opioids

were approached to take part in the study and all agreed. Referrals to the tertiary unit came from all over the UK. This group completed the study while awaiting treatment in the pain unit.

The drug abusers included in the study were taken from consecutive cases attending a methadone maintenance programme in a major London teaching hospital, serving a local South London population. All drug addicts approached to take part in the study agreed. The drug addicts admitted use of illicit drugs while on the programme, however their estimate of total amount in 24 hours is probably an underestimate.

The following information was collected:

1. Demographic data and drug use:at entry to the study

- basic medical and personal information
- past psychiatric history
- drug regimen
- use of unprescribed drugs
- HAD score (repeated monthly), this has 7 anxiety and 7 depression questions

2. Assessments

i) Initial questions at entry:

- reasons for taking opioids, using visual analogue scales (V.A.S.) e.g. to relieve pain, to calm, to help sleep, to feel good . . .
- fears about opioids - free text
- prompts to take next dose based on opioid withdrawal symptoms scale (S.O.W.S) in addition to questions relating to pain and breathlessness (Yes or No answers)
- maximum daily opioid dose in past week
- pain severity; now and average over past week (V.A.S.)

- pain distress; now and average over past week (V.A.S.)
- opioid side-effects (V.A.S) (drowsiness, constipation, nausea, vomiting)
- disturbed sleep (V.A.S.)

ii) Daily diary (for the first week only); (completed in evening and refers to that day)

- pain severity (V.A.S.)
- pain distress (V.A.S.)
- opioid side-effects (V.A.S)
- general well-being (V.A.S)
- Regular opioid dose
- extra opioid used
- effect of medication (V.A.S) - regular and extra
- other drugs used
- questions relating to anxiety and emotions

iii) Weekly diary (for up to 2 years in cancer patients, however for first month only in other groups):

- maximum dose of opioid take in 24 hour period over this week
- questions as per daily diary

iv) Follow-up questions (monthly for 3 months and up to 2 years in some cancer patients)

- preoccupation with opioids (V.A.S.)
- effect of opioids on mood (V.A.S.)
- questions from Severity of Dependence Scale (S.D.S.)

- prompts for taking next dose; S.O.W.S. questions in addition to pain and breathlessness questions (Yes/No replies)
- desires regarding opioid dose changes
- reasons for using opioids (V.A.S.)

Oral morphine equivalent dose was calculated using accepted conversion ratios. Correlation between daily morphine equivalent dose and age, ratings of pain, opioid efficacy and mood were calculated by Spearman and Pearson correlation coefficients separately for each group.

These data were collected over the following

1. initially at entry into the study
2. daily for 1 week - (questions relating to drug doses, effectiveness, reasons for taking dose, side-effects)
3. weekly for 4 weeks
4. monthly for 3 months

The questionnaires were completed by the cancer pain patients who were mostly out-patients during review (the daily diary was completed between visits).

The chronic pain patients returned the questionnaires in a pre-paid envelope, following completion of initial questionnaires in the Pain Unit.

The drug abusers completed the initial questionnaires at the methadone maintenance clinic and the remainder during attendance at the Day Unit.

The statistics package, S.P.S.S. 6.01 for windows was used to analyse the data and plot graphs to give a visual impact of: dose, effect of dose, pain and side-effects of opioids over time. In addition, the results from the statistical analysis described in chapter 3 were studied from the point of tolerance to analgesia and tolerance to opioid side-effects.

Results

Fourteen cancer patients, 27 chronic non-malignant pain patients and 30 drug abusers entered the study. They had been using opioids for a mean of 6 months, 2.2 years and 13 years respectively, in median daily oral morphine equivalent doses of 1320 mg, 700 mg and 160 mg. Cancer and chronic pain patients had mean ages of 59 years and 43 years, drug abusers were younger, mean age, 34 years.

The mean dose efficacy for cancer patients was inversely related to mean ratings of pain severity, ($r = 0.762$, $p<0.025$) and distress, ($r = 0.767$, $p<0.025$), but not to maximum pain severity and distress, ($r = 0.045$, $r = 0.533$). (Time scale, 3 months to 2 years, mean 6 months).

The mean dose efficacy for chronic non-malignant pain patients was unrelated to mean or maximum pain severity ($r = 0.192$, $r = 0.088$) or pain distress ($r = 0.034$, $r = 0.053$). (Time scale, 3 months).

No relationship could be found between mean or maximum ratings of dose efficacy and any other variable for drug users. (Time scale, 3 months).

Clinical tolerance to the side-effects of opioids in the 3 groups was as follows:

There was no linear relationship between oral morphine equivalent dose and the mean daily scores over the first week of the daily diary of constipation, sedation, nausea and vomiting.

Drug abusers without pain had significantly less constipation than drug abusers with pain or both pain groups in this study. This raises the unanswered question of the role of pain in gut motility.

Discussion

In the cancer pain group the efficacy of opioid on pain severity was significant; greater the efficacy, the less the pain severity. This is an anticipated desired effect. The patients with chronic non-malignant pain also showed significant efficacy if opioid was taken regularly otherwise efficacy was unpredictable. A regular opioid regimen is expected to improve analgesic efficacy. There was no relationship between opioid dose and efficacy in both pain groups; this would be expected due to the complexities of the pain syndromes. Frequently higher opioid doses are required for neuropathic pain syndromes.[9]

On the other hand drug abusers described less effects i.e. clinical tolerance, with the opioid the higher the dose. This describes clinical tolerance to the desired effect of opioids in drug abusers but not in the patients with pain.

Clinical tolerance to both the wanted and unwanted effects of opioids is a fascinating phenomenon made up of complex components. In this study there was no evidence of analgesic tolerance in the cancer pain patients nor in chronic non-malignant pain patients. The former had remarkably static opioid doses, responses to dose and pain control over a period of up to 2 years, (mean, 6 months), the maximum period of data collection. The non-malignant pain group had more chaotic use of opioids than the cancer pain patients, however the plots show (p77-82) very clearly that this is chaos not tolerance. The pain groups had been using opioids for a mean of 6 months and 2.2 years respectively at the study entry. In contrast, the drug abuser group had clear evidence of tolerance to the hedonistic effects of opioids and had been using them for a mean of 13 years.

The fact that none of the common opioid adverse effects were related to opioid dose is interesting. Since there was no opioid dose relationship with side-effects to opioids in any group, this implies the development of tolerance to these effects at any given opioid dose for an individual. The side-effects

of opioids in the chronic dosing situation are accepted as initiation effects and are likely to increase or recur with an increase in opioid dose.

Traditionally it has been said that constipation is opioid dose related [10] although we have previously described no relationship between opioid dose and constipation[11]. This data once again supports no relationship between opioid dose and constipation.

In addition the data also supports the belief that drug addicts do not walk about the streets constipated. This group do develop more tolerance to constipation than cancer or chronic pain patients, unless pain is also present in the drug addict. The phenomenon of pain and constipation is interesting and may relate to obvious factors such as immobility and poor dietary intake or to less obvious factors such as tachykinins involved in the soup of neurotransmitters in pain, adversely affecting gut motility [12].

The fact that clinically relevant pharmacological tolerance is generally accepted not to be an issue in cancer pain management is backed by this data. Similarly no evidence of tolerance is seen in non-malignant pain patients. The plots of opioid use, pain and effects are demonstrated here for 2 cancer pain patients and 2 chronic non-malignant pain patients (p 68-76) cases 39 and 41 are cancer patients and cases 61 and 62 are chronic non-malignant pain patients. These plots are representative of each of these pain groups in the study. The remaining plots are in the disc at the back of this thesis.

Conclusions

There is no evidence of pharmacological tolerance to the analgesic effect of opioids, no matter how high the dose required, in the cancer pain patients in this study. Constant doses can be used for long periods of time - up to 2 years in one patient in this study. It is similarly interesting to note that in the chronic non-malignant pain group, use of opioids can be more chaotic than in cancer pain, however there is no evidence of a gradually increasing dose over time and dose/efficacy relationships remain on the whole chaotic and unpredictable.

This is in contrast to the drug addicts who we know to require increasing doses to achieve the same effects over time.[4] In this study the drug addicts described fewer desired effects the larger the dose, reinforcing our knowledge on pharmacological tolerance in this group.

These results clearly also demonstrate that pharmacological tolerance does occur to opioid adverse effects.

This is important data from the point of view of education and practical care of patients.

Current work is under way to look more precisely at the rate of development of tolerance to the opioid side-effects of different opioids.

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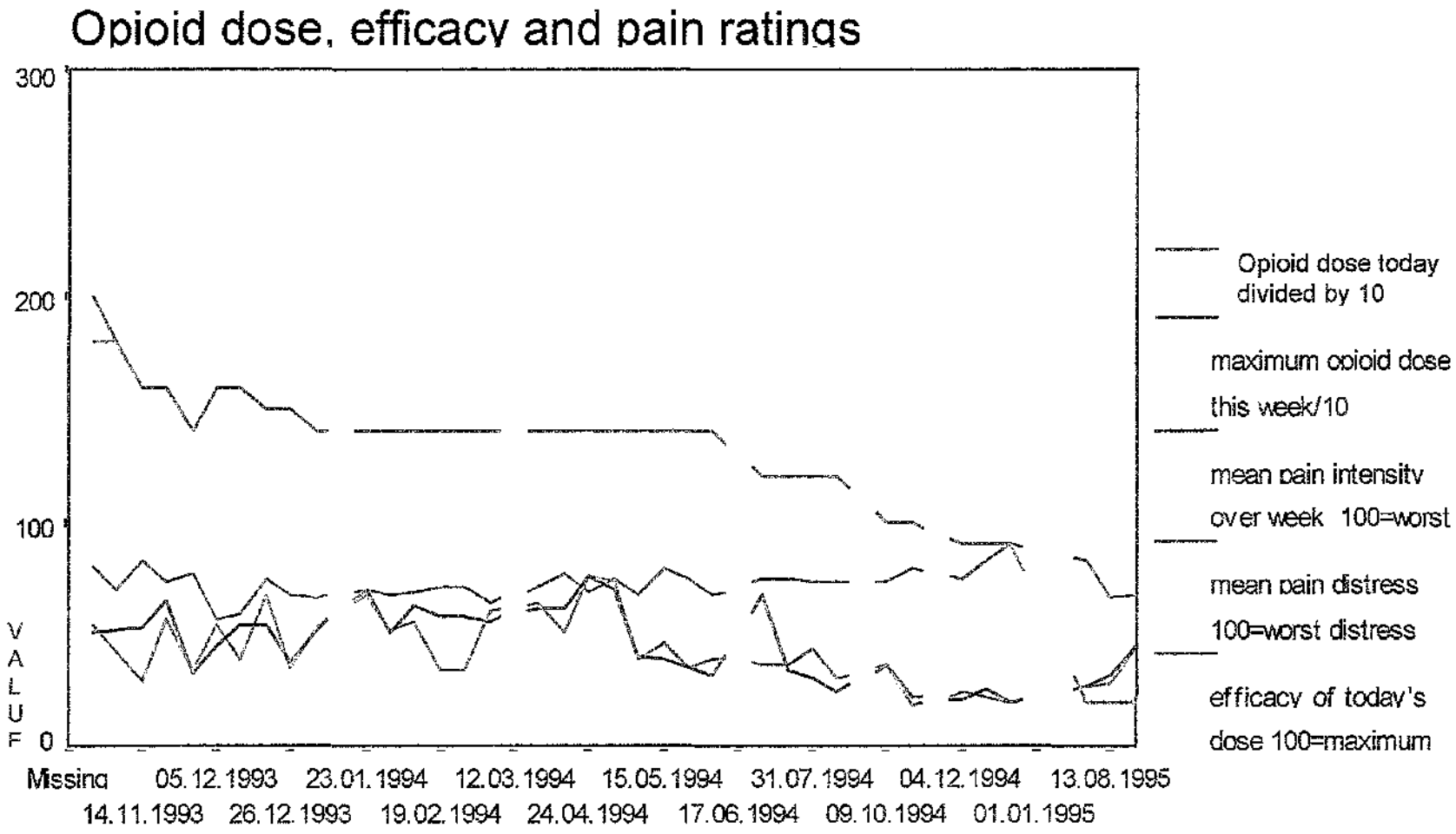
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300
200
100
0
VALUE
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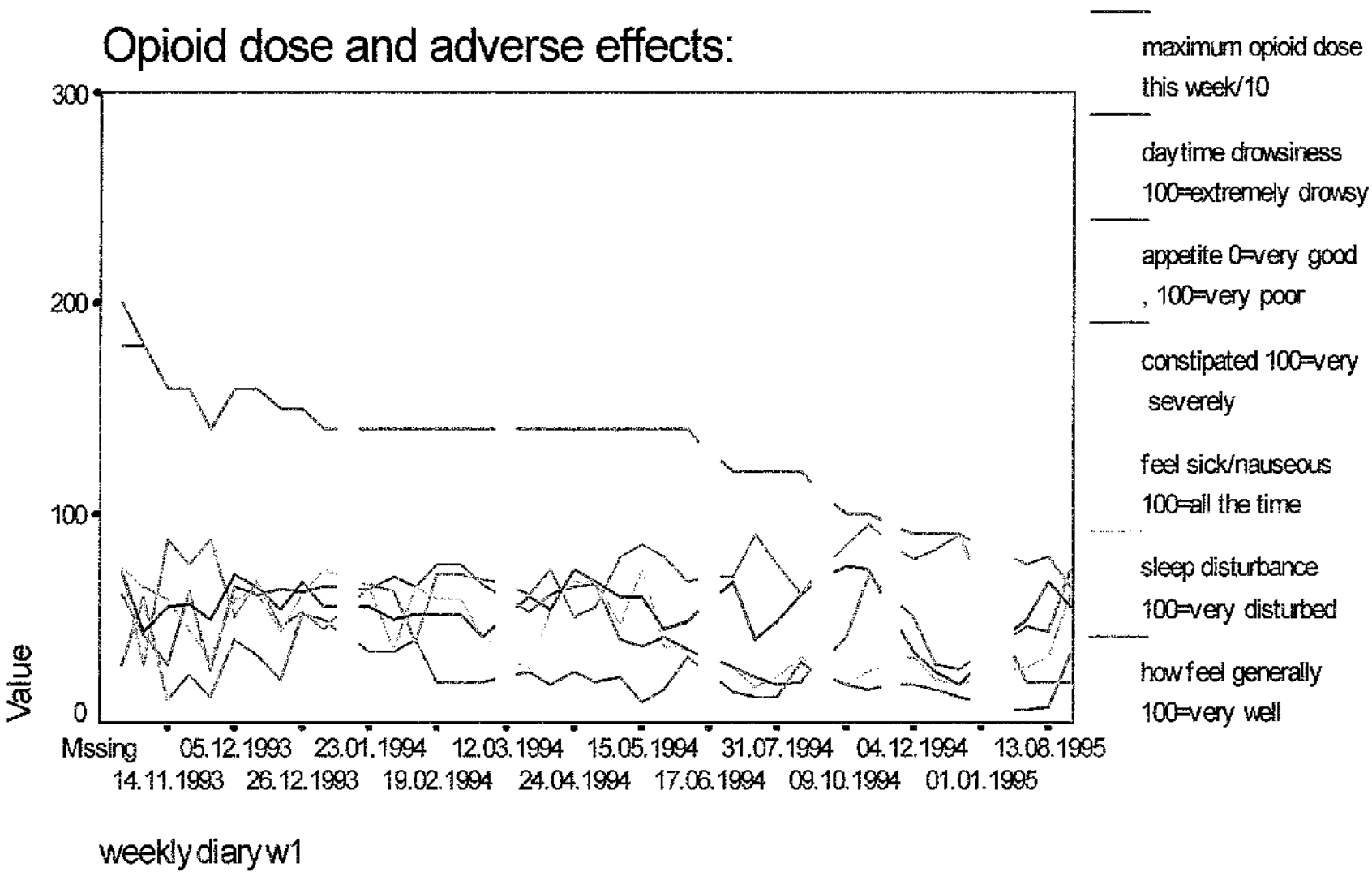
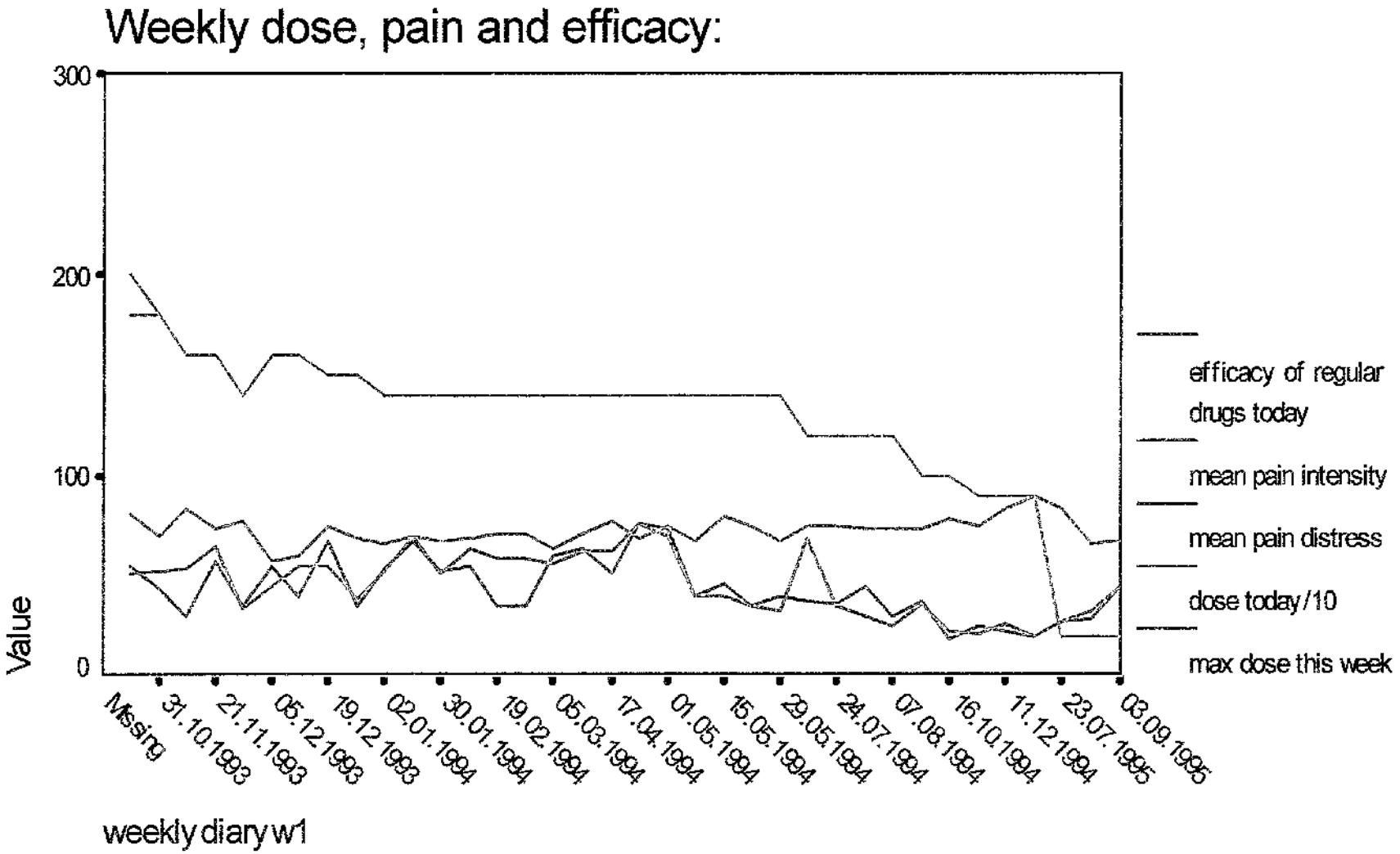
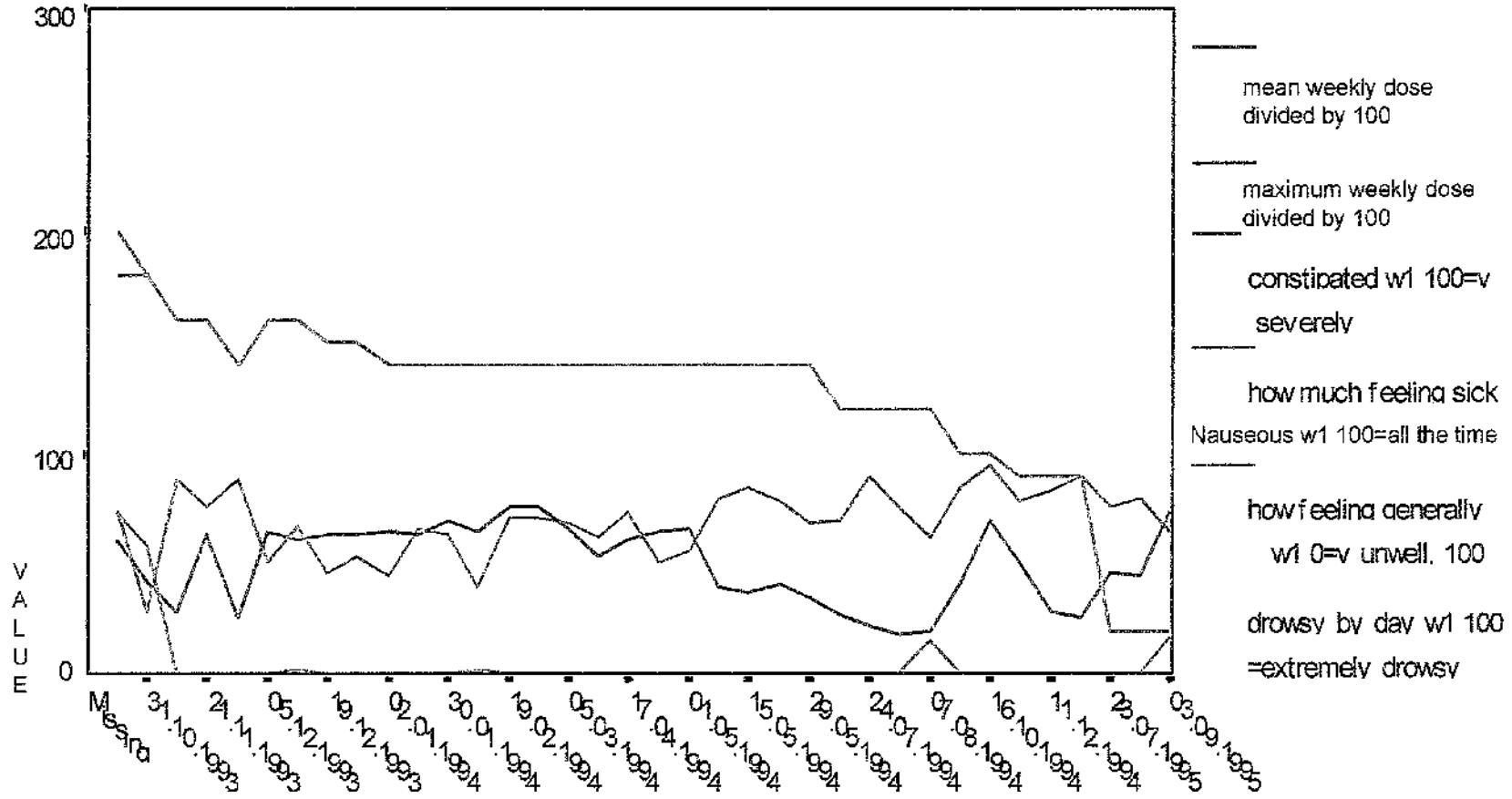
14.11.1993
05.12.1993
26.12.1993
23.01.1994
19.02.1994
12.03.1994
24.04.1994
15.05.1994
17.06.1994
31.07.1994
09.10.1994
04.12.1994
01.01.1995
13.08.1995
Opioid dose today divided by 10
maximum opioid dose this week/10
mean pain intensity over week 100=worst
mean pain distress 100=worst distress
efficacy of today's dose 100=maximum
weekly diary w1

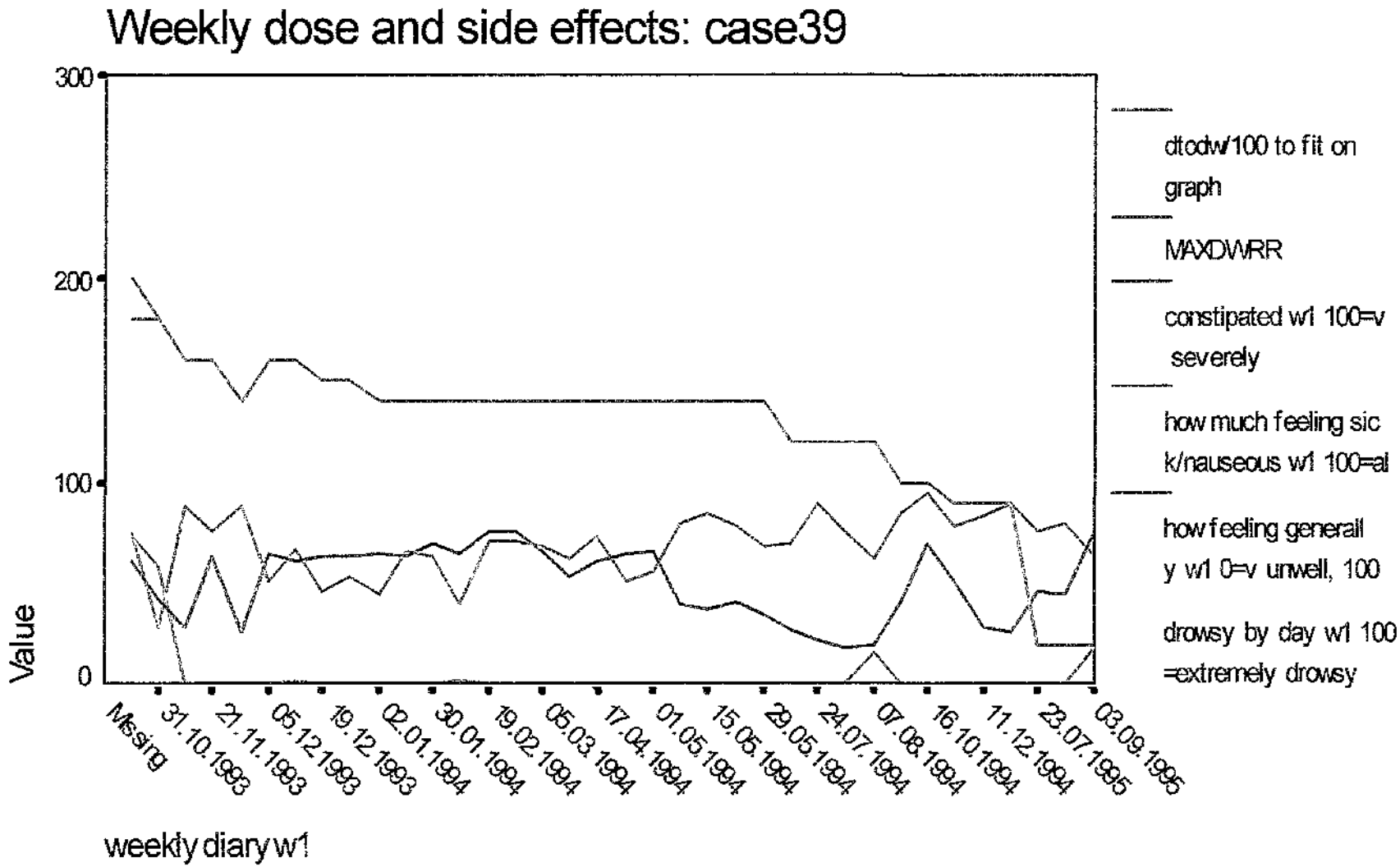

Opioid dose and adverse effects:
300
200
100
0
Value
Mssing
14.11.1993
05.12.1993
26.12.1993
23.01.1994
19.02.1994
12.03.1994
24.04.1994
15.05.1994
17.06.1994
31.07.1994
09.10.1994
04.12.1994
01.01.1995
13.08.1995
weekly diary w1
maximum opioid dose this week/10
daytime drowsiness 100=extremely drowsy
appetite 0=very good , 100=very poor
constipated 100=very severely
feel sick/nauseous 100=all the time
sleep disturbance 100=very disturbed
how feel generally 100=very well

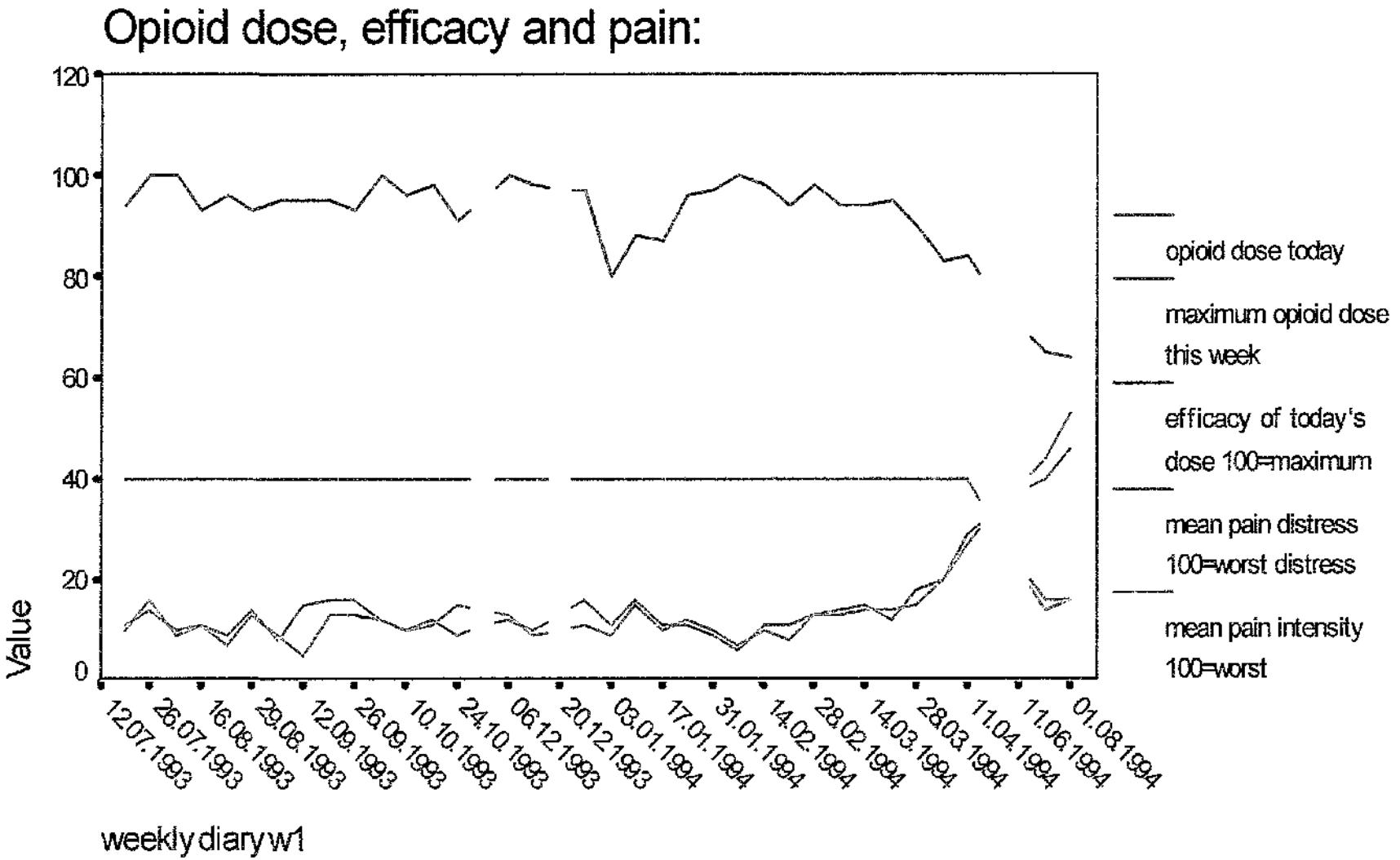

Weekly dose, pain and efficacy:
300
200
100
0
Value
Missing
31.10.1993
21.11.1993
05.12.1993
19.12.1993
02.01.1994
30.01.1994
19.02.1994
05.03.1994
17.04.1994
01.05.1994
15.05.1994
29.05.1994
24.07.1994
07.08.1994
16.10.1994
11.12.1994
23.07.1995
03.09.1995
weekly diary w1
efficacy of regular drugs today
mean pain intensity
mean pain distress
dose today/10
max dose this week

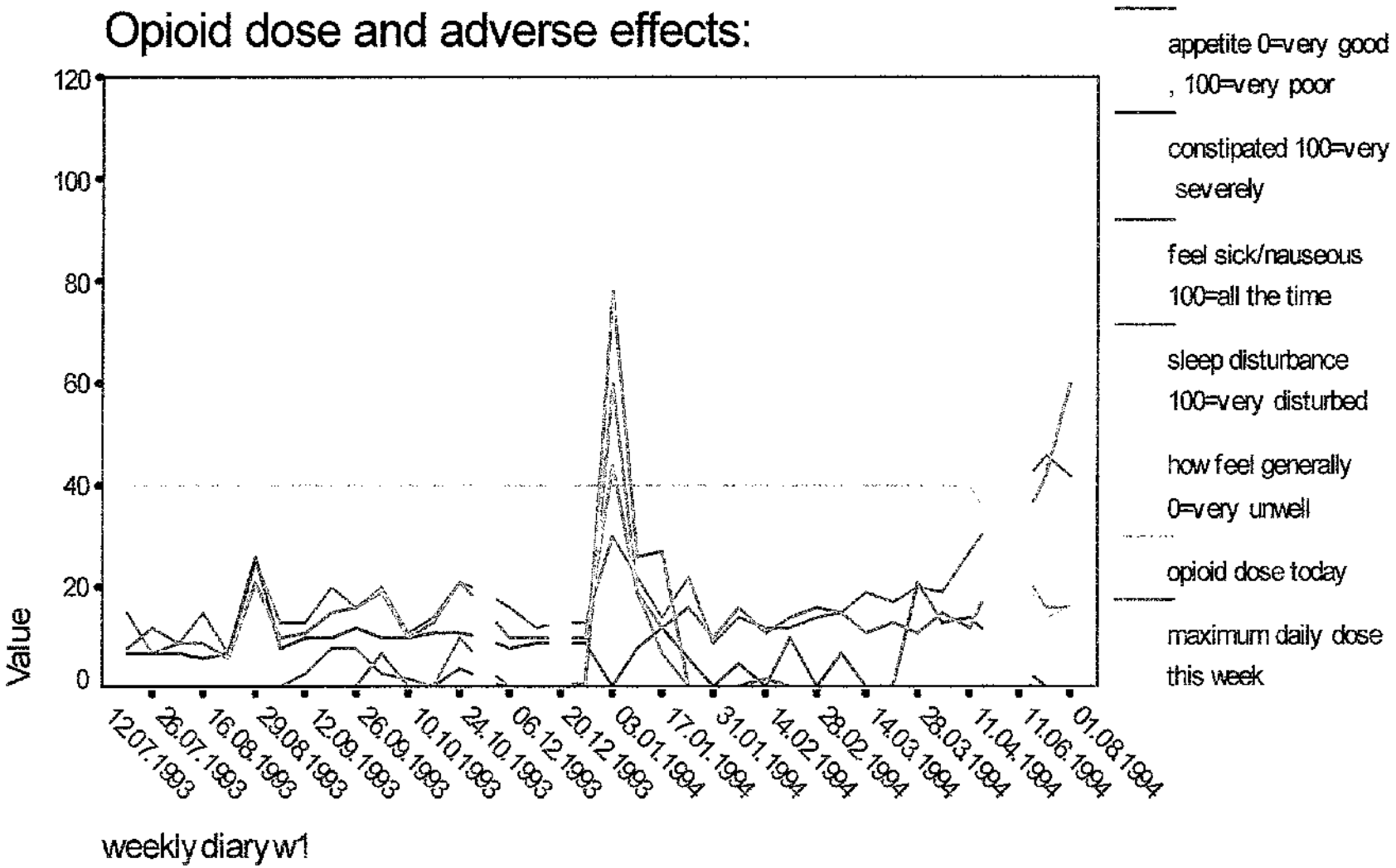
Weekly dose and side effects:

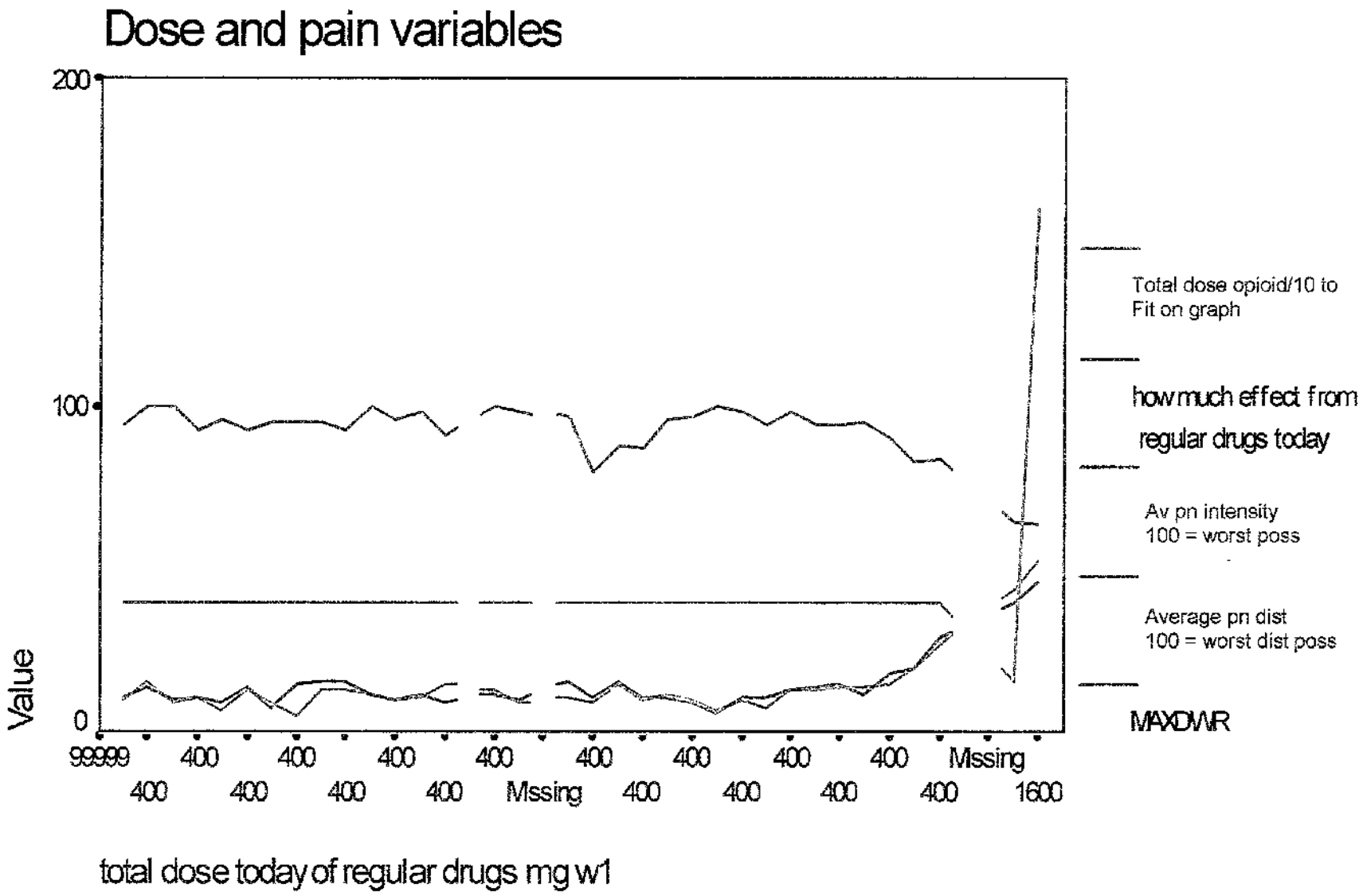


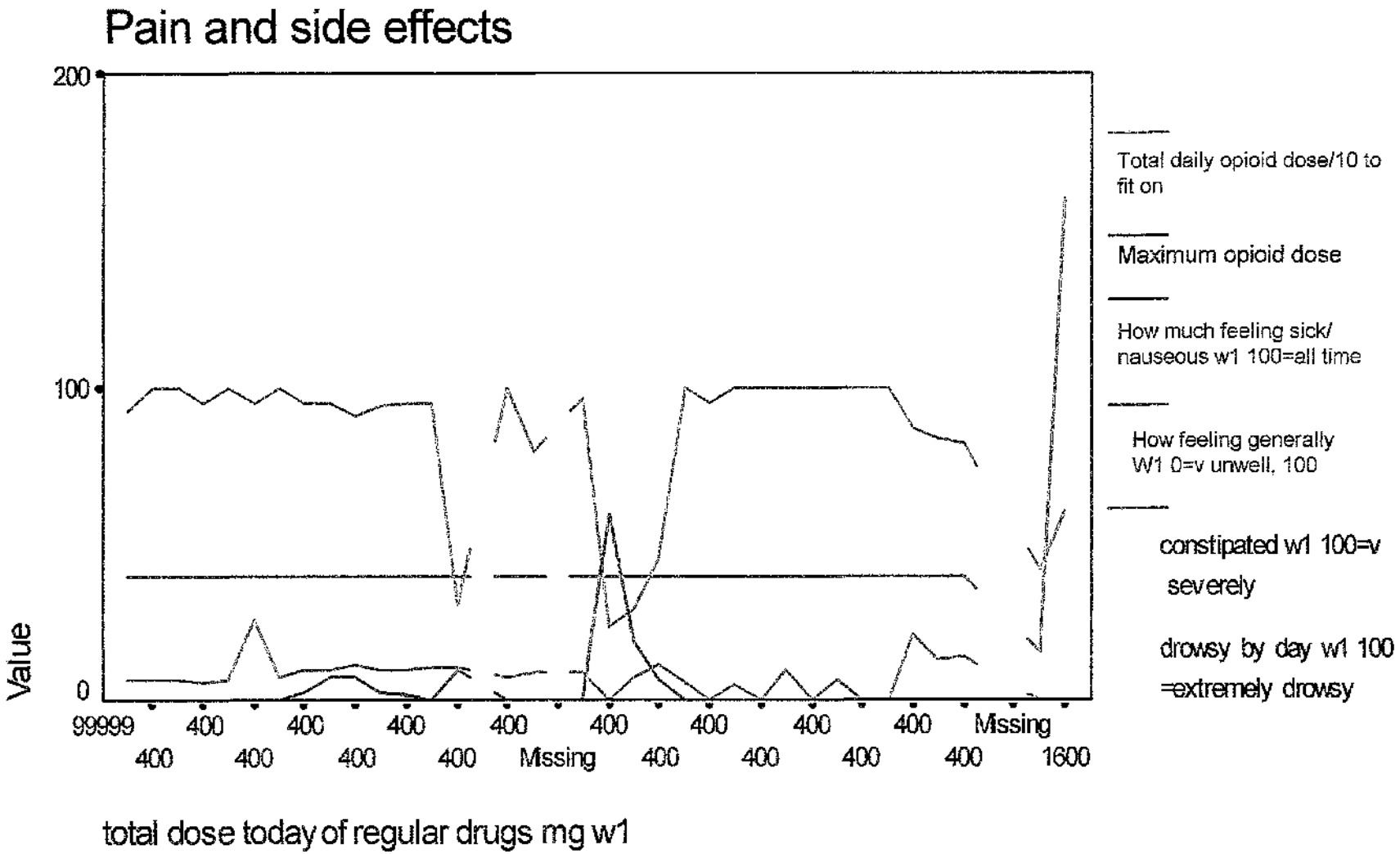
weekly diary w1


Weekly dose and side effects: case39
300
200
100
0
Value
dtodw/100 to fit on graph
MAXDWRR
constipated w1 100=v severely
how much feeling sick/nauseous w1 100=al
how feeling generally w1 0=v unwell, 100
drowsy by day w1 100 =extremely drowsy
Missing
31.10.1993
21.11.1993
05.12.1993
19.12.1993
02.01.1994
30.01.1994
19.02.1994
05.03.1994
17.04.1994
01.05.1994
15.05.1994
29.05.1994
24.07.1994
07.08.1994
16.10.1994
11.12.1994
23.07.1995
03.09.1995
weekly diary w1

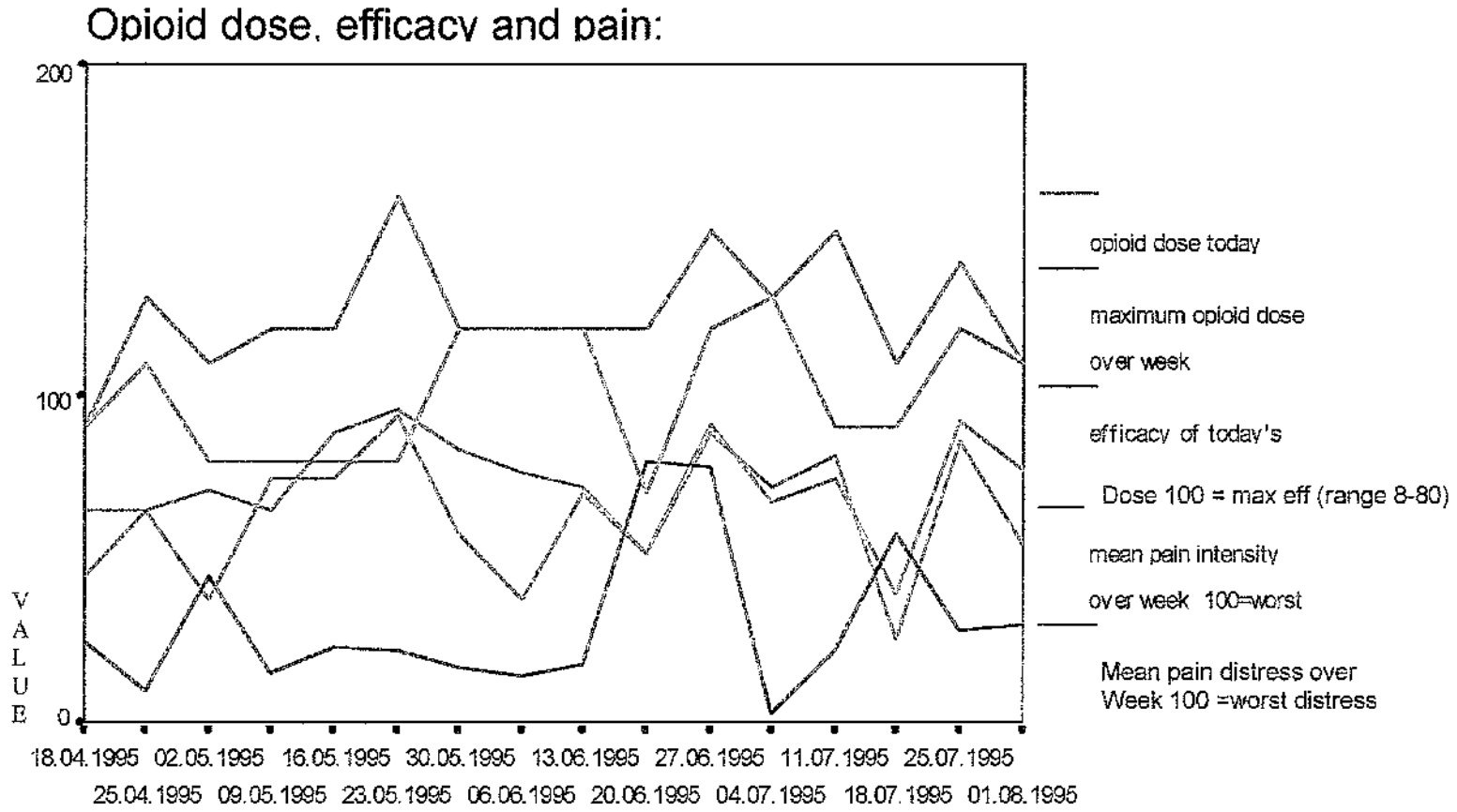

Opioid dose, efficacy and pain:
120
100
80
60
40
20
0
Value
12.07.1993
26.07.1993
16.08.1993
29.08.1993
12.09.1993
26.09.1993
10.10.1993
24.10.1993
06.12.1993
20.12.1993
03.01.1994
17.01.1994
31.01.1994
14.02.1994
28.02.1994
14.03.1994
28.03.1994
11.04.1994
11.06.1994
01.08.1994
weekly diary w1
opioid dose today
maximum opioid dose this week
efficacy of today's dose 100=maximum
mean pain distress 100=worst distress
mean pain intensity 100=worst


Opioid dose and adverse effects:
120
100
80
60
40
20
0
Value
12.07.1993
26.07.1993
16.08.1993
29.08.1993
12.09.1993
26.09.1993
10.10.1993
24.10.1993
06.12.1993
20.12.1993
03.01.1994
17.01.1994
31.01.1994
14.02.1994
28.02.1994
14.03.1994
28.03.1994
11.04.1994
11.06.1994
01.08.1994
weekly diary w1
appetite 0=very good , 100=very poor
constipated 100=very severely
feel sick/nauseous 100=all the time
sleep disturbance 100=very disturbed
how feel generally 0=very unwell
opioid dose today
maximum daily dose this week

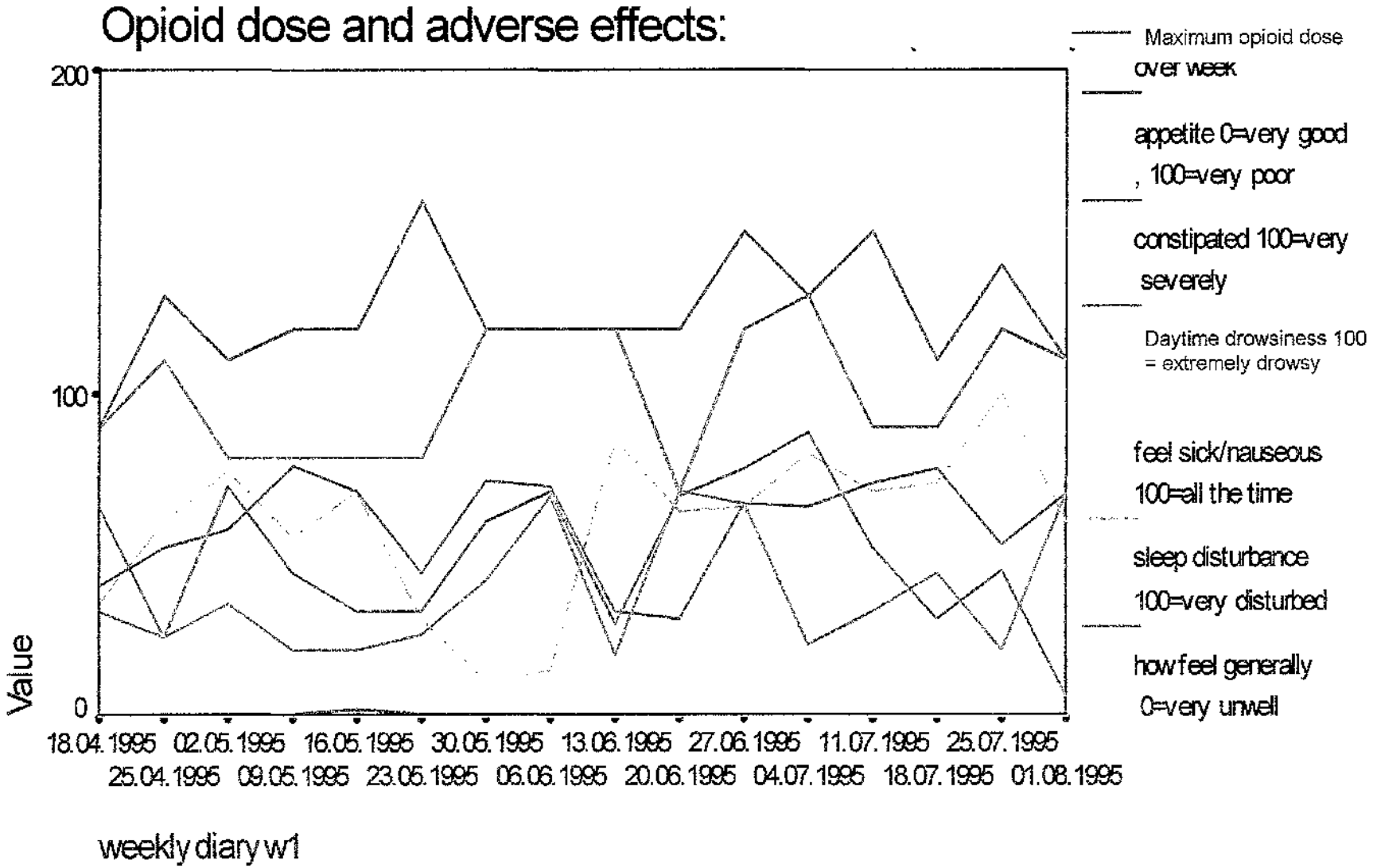

Dose and pain variables
200
100
0
Value
99999
400
Missing
1600
Total dose opioid/10 to Fit on graph
how much effect from regular drugs today
Av pn intensity 100 = worst poss
Average pn dist 100 = worst dist poss
MAXDWR
total dose today of regular drugs mg w1


Pain and side effects
200
100
0
Value
99999
400
400
400
400
400
400
400
400
400
Missing
400
400
400
400
Missing
400
400
400
400
1600
total dose today of regular drugs mg w1
Total daily opioid dose/10 to fit on
Maximum opioid dose
How much feeling sick/ nauseous w1 100=all time
How feeling generally W1 0=v unwell, 100
constipated w1 100=v severely
drowsy by day w1 100 =extremely drowsy

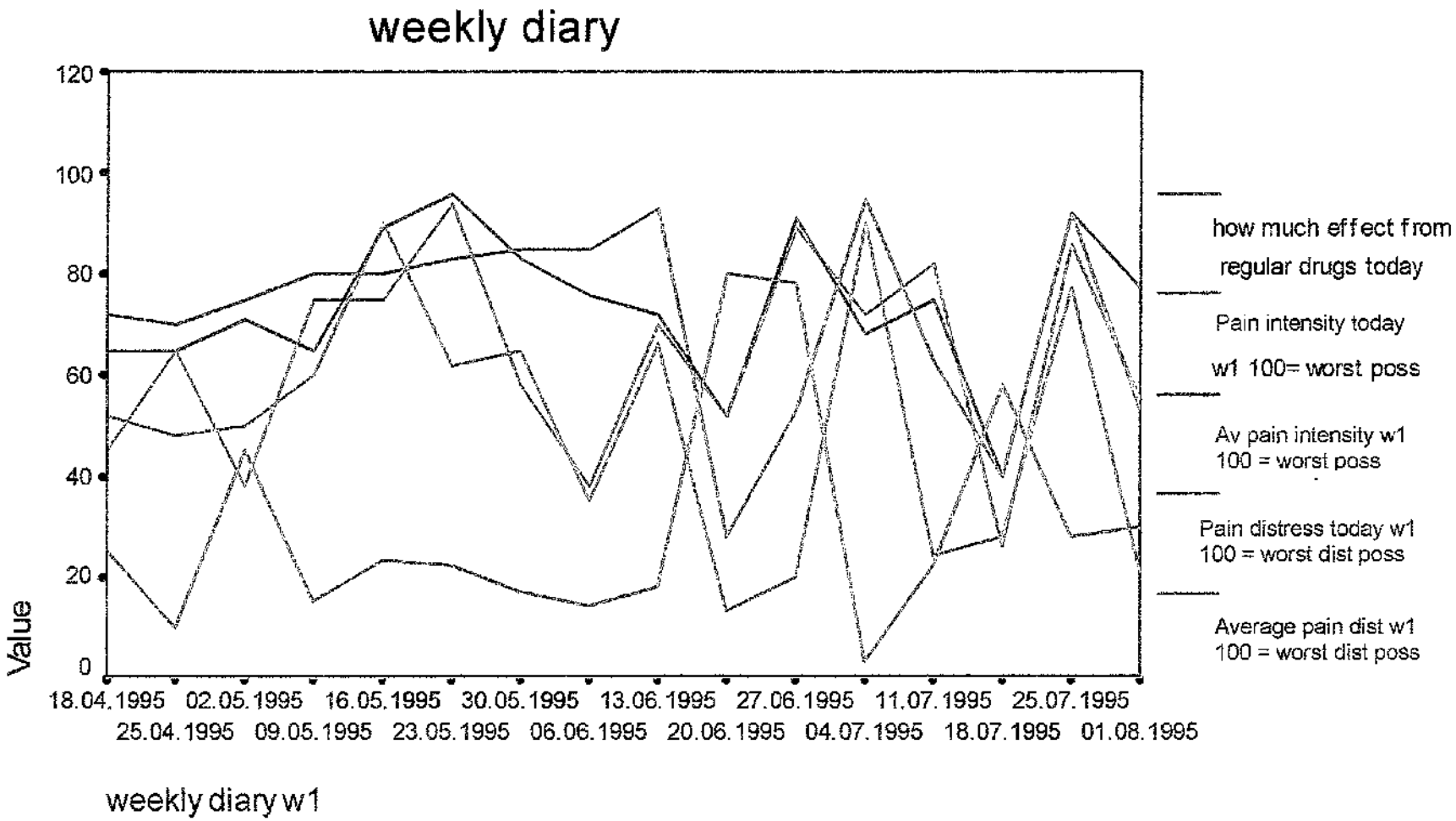
Case 61 (chronic pain)



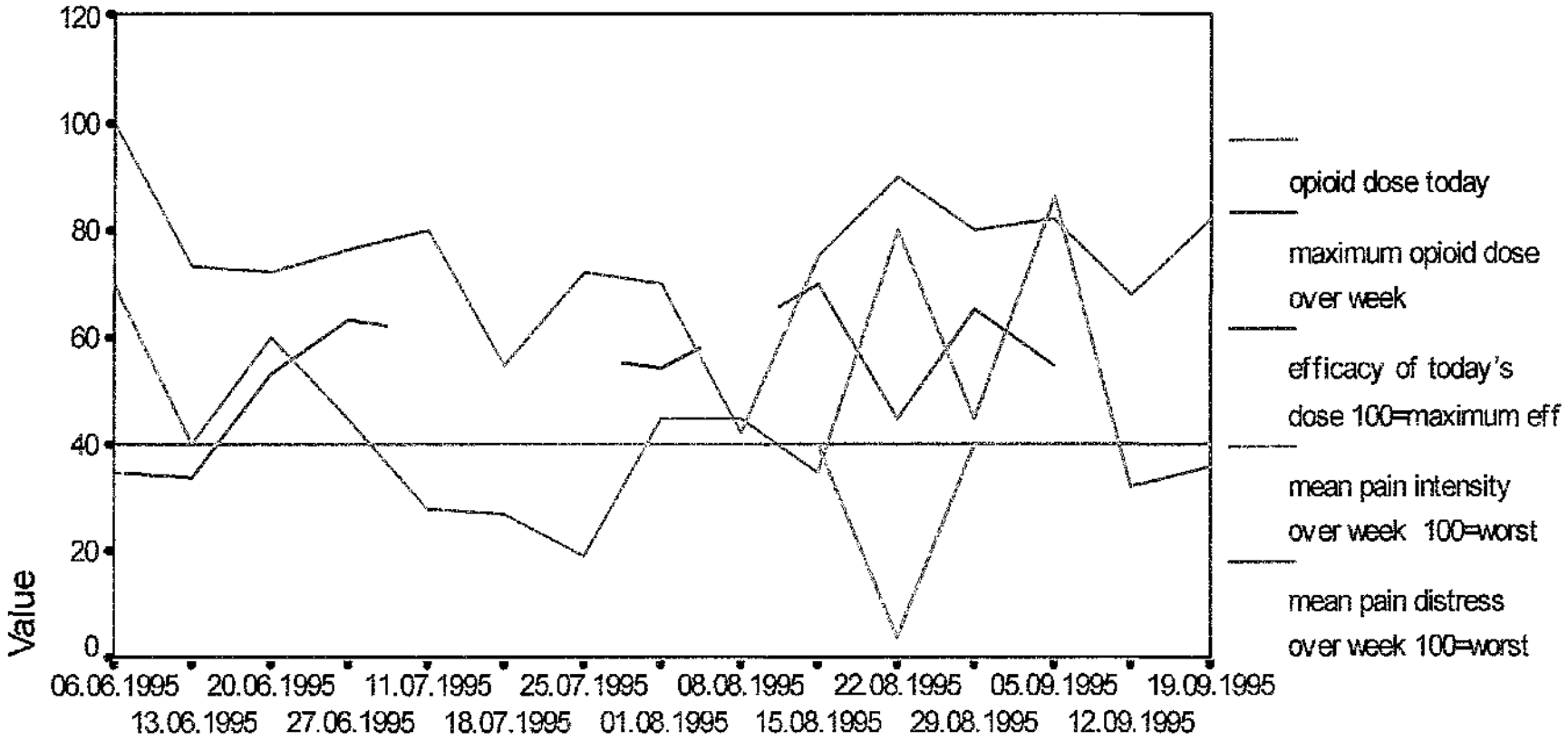
Case 61 (chronic pain)



Case no 61


weekly diary
120
100
80
60
40
20
0
Value
18.04.1995
25.04.1995
02.05.1995
09.05.1995
16.05.1995
23.05.1995
30.05.1995
06.06.1995
13.06.1995
20.06.1995
27.06.1995
04.07.1995
11.07.1995
18.07.1995
25.07.1995
01.08.1995
weekly diary w1
how much effect from regular drugs today
Pain intensity today w1 100= worst poss
Av pain intensity w1 100 = worst poss
Pain distress today w1 100 = worst dist poss
Average pain dist w1 100 = worst dist poss

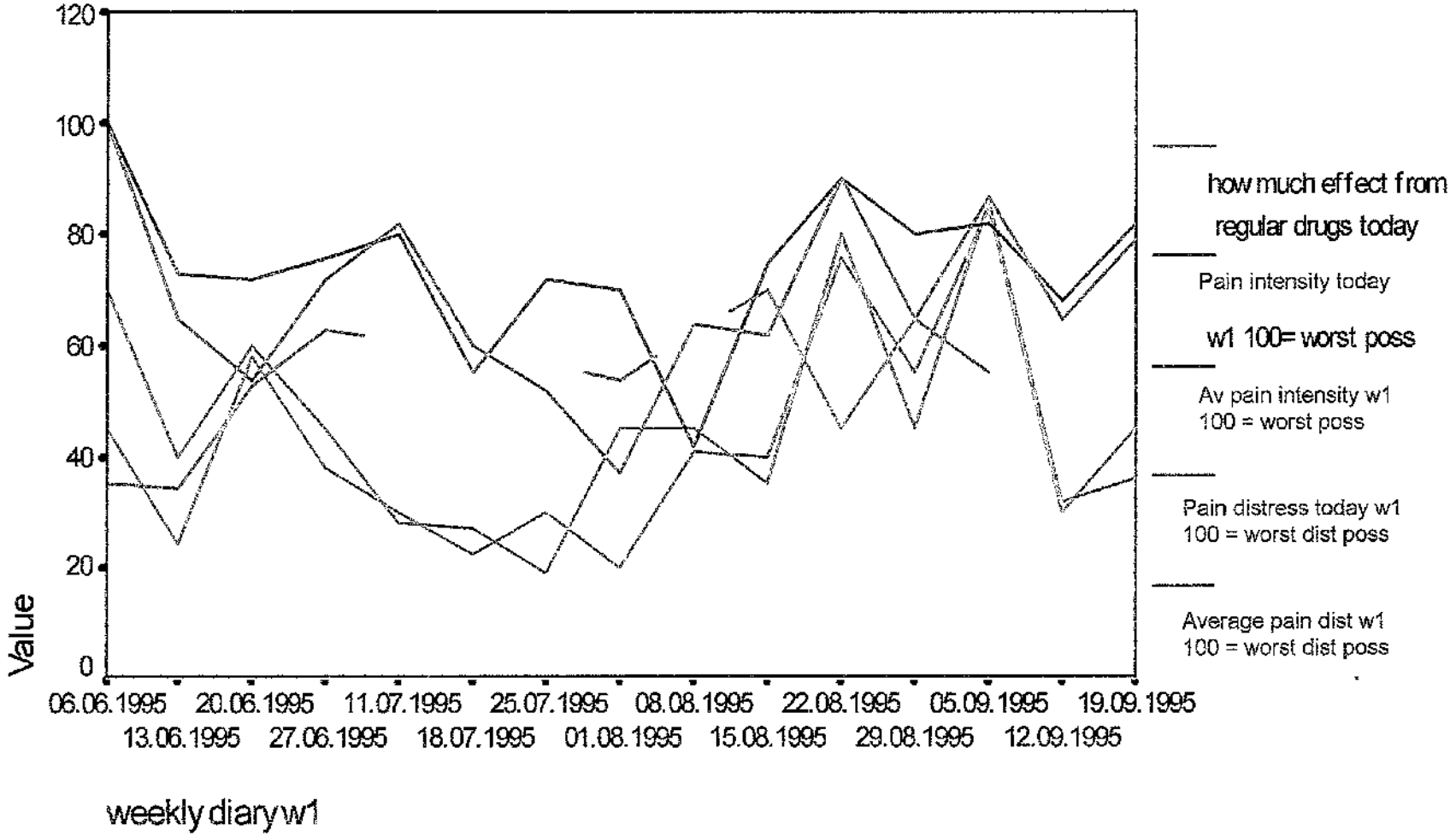
Opioid dose, efficacy and pain:



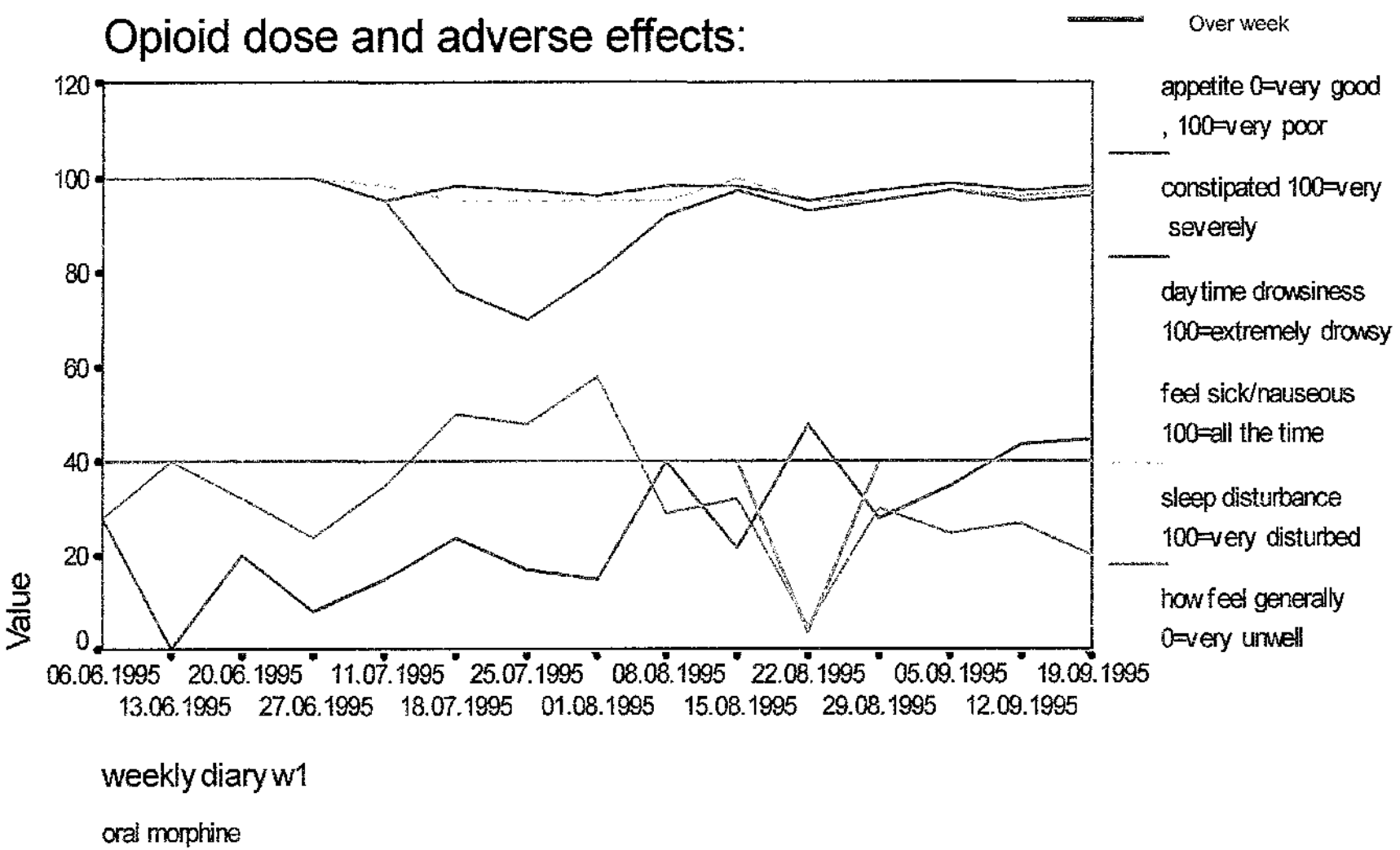
weekly diary w1

oral morphine

Pain and opioid efficacy over weeks:



Case 62 (chronic pain)



Chapter 5

Do patients who have received intravenous opioids post-bone marrow transplant (B.M.T.) develop physical dependence?

Physical dependence on opioid analgesics is manifest by withdrawal symptoms if the drug is abruptly discontinued or an antagonist is administered. The prevalence of physical dependence associated with the therapeutic use of opioids is not known.

It is well recognised anecdotally that some patients may be able to withdraw therapeutic opioids abruptly, even after taking them for long periods of time, whereas others may exhibit clear cut physical symptoms of withdrawal. This has been a source of great confusion in the past because physical dependence used to be equated with addiction whereas we now regard it as just one component of addiction, the most important component being psychological dependence or drug craving. Clearly the presence of physical dependence without psychological dependence can occur in the absence of addiction.

The general belief which has evolved is that patients who have received analgesic doses of opioids for up to two weeks may be able to discontinue the drug with only mild symptoms, usually not attributed by either patients or physician to withdrawal. It is said that in most instances, the major complaint is slight irritability and difficulty in sleeping. This has however never been systematically examined.

In contrast, an individual using opioids primarily for euphoric effects may develop withdrawal symptoms as soon as the scheduled time for the next dose has passed.

The characteristics and intensity of withdrawal symptoms vary greatly and may be influenced by a variety of factors as the specific drug used: dosage, intervals between dosage, duration of use, and even one's

psychological state. It is helpful to distinguish between those signs and symptoms considered to be oriented toward obtaining an opioid drug (purposive) and those that can be objectively evaluated and are independent of the environment or psychological state of the patient (nonpurposive).[1] These phenomena have been described in relation to drug addicts and not the patient using opioids for therapeutic reasons.

Purposive phenomena can appear quite early. The earliest symptom is anxiety, usually manifested by drug-seeking behaviour, which in the clinical setting takes the form of immediate requests for additional analgesia. Purposive behaviour usually reaches peak intensity by 36 to 72 hours following the last diamorphine injection. It can be modified greatly not only by the environment but also by the presence of a calm sympathetic observer.

Nonpurposive symptoms appear 8 to 12 hours after the last diamorphine injection. The intensity of symptoms may be considered mild, moderate, marked or severe (tables II & III). Mild symptoms result from early autonomic hyperactivity, which may increase in intensity over the first day and then stabilise as the syndrome progresses. During the time, pupillary dilation, loss of appetite, tremor, and the appearance of 'gooseflesh' due to piloerecta stimulation will occur. At 16 to 18 hours, if an opioid has not been administered, the individual may fall into a restless, tossing sleep for two to three hours called the 'yen'. On awakening, approximately 20 hours after the last dose, there is further evidence of withdrawal consisting of marked restlessness, deep breathing, fever and insomnia. Hypertension is not infrequent, and complaints of chills alternating with flushing and vomiting and diarrhoea may appear in two-thirds of people. Severe muscular spasms in the extremities were responsible for the origin of the term 'kicking the habit', describing heroin withdrawal. Abdominal cramps and bone pain can occur.[2]

The intensity of withdrawal varies greatly with the specific opioid, as well as dose administered. In general, short acting opioids tend to produce brief intense abstinence syndromes, whereas those drugs that are slowly eliminated produce mild withdrawal. With morphine and diamorphine, peak intensity is reached

at 36 to 48 hours, continuing at a plateau for up to 72 hours and gradually subsiding over the next five to ten days.

Methadone withdrawal presents a syndrome that develops much more slowly without ever reaching the severity seen with morphine. Symptoms rarely occur before 48 hours after the last dose but can last for several weeks.[1]

While acute withdrawal symptoms usually last only 2-3 days, a low-grade protracted abstinence syndrome characterised by generalised mild discomfort, poor sense of well-being, and drug craving is well described.[2]

It has been postulated that individuals with chronic pain who use frequent doses of short-acting opioids on a regular basis may become physically dependent and develop intermittent withdrawal phenomena, including sympathetic arousal, increased muscular tension and receptor 'hunger' between doses of medications.[3] These intermittent withdrawal phenomena - or on-off phenomena - may act to increase pain during periods of receptor hunger. Use of longer acting medications, such as methadone, levorphanol, or controlled-release morphine, could theoretically avoid such withdrawal phenomena by providing continuous, relatively stable blood levels of opioids.

While on the one hand if the potential for on-off phenomena is eliminated, physical dependency itself may represent an inconvenience, on the other hand, it is associated with very negative feelings in prescriber and in patients. Fear of a physical withdrawal syndrome can compromise adequate opioid analgesia in some acute settings e.g. intensive care, paediatric intensive care and post-operative analgesia, as well as in chronic pain, including cancer pain management.[4, 5, 6]

The prevalence of physical dependence associated with the therapeutic use of opioids is not known. There is likely to be a spectrum of physical dependence relating to many variables, however, we wanted to

examine this phenomenon in a group of patients with severe pain lasting days to weeks, as in some intensive care or post-operative pain situations.

Patients who receive a bone marrow transplant (B.M.T.) form a homogenous group with a predictable cause and duration of pain. B.M.T. usually follows high dose chemotherapy and radiotherapy and patients develop a painful mucositis, most severely affecting the mouth causing painful swallowing. This is unavoidable, and can last for one to three weeks. Ninety-five per cent of patients will require intravenous diamorphine (the strong opioid of choice in this situation in the U.K.) for some or all of this time. Classically when the mucositis pain resolves these patients discontinue the opioid abruptly hence making an ideal group in whom to study opioid withdrawal symptoms.

Aim:

To establish the presence of any signs and symptoms of withdrawal from strong opioids in patients who have received intravenous diamorphine by continuous infusion for the treatment of pain due to oropharyngeal mucositis post-B.M.T. In addition pain and functional disability caused by oropharyngeal mucositis post-B.M.T was monitored.

Methods:

Ethical approval for the study was obtained from U.B.H.T., Bristol. Patients were recruited from a bone marrow transplant unit. Consecutive patients were approached pre-transplant. All consecutive patients gave written informed consent (or assent in case of children, in presence of a parent).

There is no scale for opioid withdrawal in patients being treated with these drugs for pain. A shortened version of the original 32-item scale developed by Gossop for withdrawal in drug abusers has been validated. This 10-item short opiate withdrawal scale (S.O.W.S.) was used in the study (Appendix 1).[7]

At the same time each day the patient completed the patient diary under supervision (by M.F). Details of previous 24 hour requirement of I.V. diamorphine, concomitant medication, intercurrent medical problems along with pulse, B.P. and temperature recordings, were documented. The patient diary included the S.O.W.S. (max score = 40), in addition to a functional swallowing assessment (5 point scale, 0 = normal, 4 = unable to swallow saliva) and a pain assessment. The pain assessment was a visual analogue scale (VAS) in all patients and a 5-point smiling faces scale in children younger than 10 years as a cross-check. Surprisingly, children in the study all gave VAS scores which were consistent with the smiling faces scale. Patients were asked for pain (worst pain present) at time of assessment. (Appendices I & II)

The data collection started on day 3 post-B.M.T. and continued until the fourth day after stopping diamorphine. All patients reduced and stopped diamorphine very quickly (within 24 hours) coinciding with resolution of mucositis. For those patients not requiring diamorphine, data collection continued for two weeks from day 3 post-B.M.T.

Analysis

Results were analysed using analysis of variance to look at relationships between diamorphine dose, pain and short opioid withdrawal score. Graphs were plotted for the main variables. (Figures I, II, III P. 93).

Results:

Twelve males and 5 females, aged 4 to 39 years (median, 18 years),completed the study. Three patients did not require intravenous diamorphine. The duration on diamorphine ranged from 5 to 19 days, median, 11 days. The median daily dose of diamorphine was 0.78 mg per kg body weight. There was no significant difference between children and adults. The median score of swallowing difficulty was 0.75 pre-diamorphine, 1.55 during diamorphine and 0 after diamorphine was discontinued. The median visual

analogue scale scores for pain were 11.25, 37.6 and 2, for the periods pre, during and after diamorphine respectively.

The S.O.W.S. median scores were 3.2, 3.25 and 2, pre, during and after diamorphine administration.

There was a statistically significant association between swallowing difficulty and diamorphine dose, ($P<0.001$)also between general pain (V.A.S.) and diamorphine dose ($P<0.001$). There was no correlation between S.O.W.S. (short opiate withdrawal score) and diamorphine dose ($P>0.4$) or duration of use ($P>0.5$). In addition, there was no significant change in withdrawal score from pre, during and post diamorphine phases. The figures I, II, III, and table I show the above.

Clinical observations were clearly also important during this study. There were no problems in any patient on discontinuing the drug.

Conclusions

In this group of bone marrow transplant patients who predictably suffered from oropharyngeal mucositis requiring treatment with intravenous diamorphine, there was no evidence of physical dependence to opioids as manifested by no evidence of an opioid withdrawal syndrome. The opioid use was short-term (up to 19 days) and total daily doses of intravenous diamorphine ranged between 0.78 and 2.24 mg/kg/day (total daily dose).

These results are of practical use in many diverse situations. Short-term opioids in the hospital setting is a situation where adequate analgesia is sometimes compromised because of fear of withdrawal symptoms which might lead to drug-seeking behaviour.

We have previously assumed that the majority of patients being treated therapeutically with opioids become physically dependent. However, none of the patients in the study became physically dependent. The S.O.W.S. is likely to be an overestimate in these patients because it includes some physical symptoms which may occur post-B.M.T. Therefore the scoring system chosen for monitoring withdrawal symptoms is not a factor in these results. The route of opioid administration is highly unlikely to have given such results since the intravenous route has been implicated in increasing the likelihood of development of physical dependence. Intravenous diamorphine (infusion or bolus) is said to start a downward path to addiction - this is not the case in this study. The duration of opioid use is also an unlikely factor; patients were on opioids for up to 19 days in this study. The dose may be an issue but unlikely; doses of up to 160 mg of intravenous diamorphine per day are significant doses.

The regimen of a continuous intravenous opioid infusion rather than bolus injections is again an unlikely explanation of lack of physical dependence.

In summary this data shows no evidence of physical dependence in this patient group and clearly shows how intravenous diamorphine can be used successfully and then abruptly discontinued. It is important that we look at these phenomena in other patient groups and try to include patients who have been using opioids for a longer duration.

Table 1

	Pre Diamorphine	**During Diamorphine**	**Post Diamorphine**
Duration (days) range 5-19 median 11			
Swallowing difficulty (medians)	0.75	1.55	0
VAS (mm) Pain (medians)	11.25	37.6	2
S.O.W.S (medians)	3.2	3.25	2

Table II

Symptoms of Opioid Withdrawal

Early	First 10 hours
Anxiety Sweating Rapid short respirations Slight rhinorrhea and lacrimation Dilated reactive pupils	
Late	**10 hour to 14 days**
Marked lacrimation and rhinorrhea Tachycardia Tremor Yawning Piloerection Nausea, vomiting, diarrhoea Abdominal pain Fever Leukocytosis Elevation of blood pressure Diffuse muscle spasm	
Prolonged	**10 days to several months**
Irritability Fatigue Bradycardia Decrease in body temperature Persistent urinary catecholamine secretion Hyposensitivity of respiratory centre to carbon dioxide	

Table III

Intensity of Withdrawal Symptoms

Mild	Moderate	Marked	Severe
Anxiety Lacrimation Rhinorrhea Sneezing Sweating Yawning	All mild signs Loss of appetite Pupillary dilation Piloerection Tremor	All moderate signs Fever Hypertension Deep breathing Nausea	All marked signs Vomiting Diarrhoea Abdominal pain Muscle spasms

Appendix I

Name:	Date:

Please put a tick in the appropriate box if you have had any of the following during the last 24 hours.

	None	Mild	Moderate	Severe
Feeling sick				
Stomach cramps				
Muscle spasms/twitching				
Feelings of coldness				
Heart pounding				
Muscular tension				
Aches and pains				
Yawning				
Runny eyes				
Insomnia/ problems sleeping				

How is your swallowing today? *Please tick the appropriate box*

	Normal
	Discomfort on swallowing
	Difficulty swallowing soft-diet
	Severe difficulty - fluids only
	Unable to swallow saliva

How is your pain today? *Please put a mark on the line*

No pain at all _____ worst pain possible

Fig I

Difficulty Swallowing

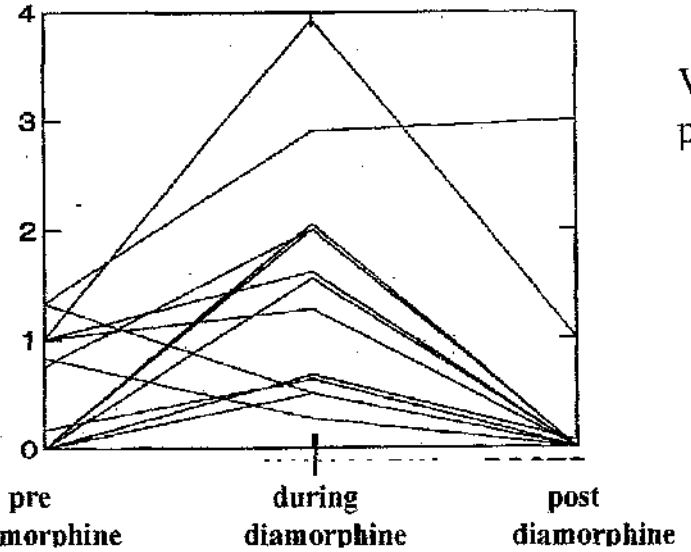


Fig II

V.A.S. for pain in mm

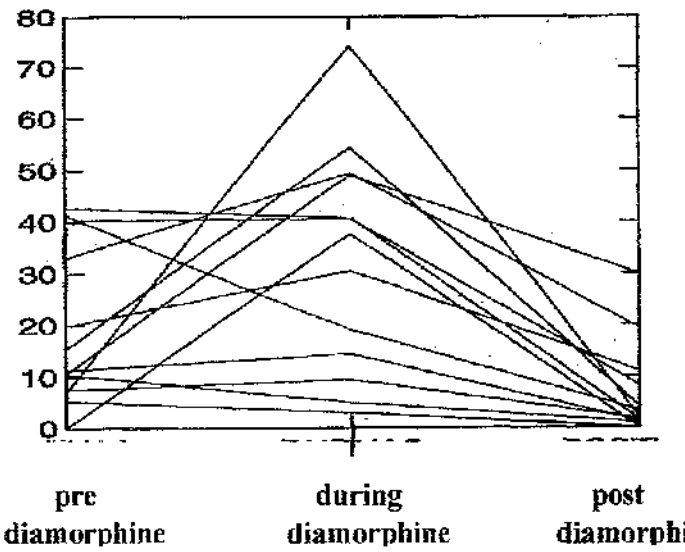
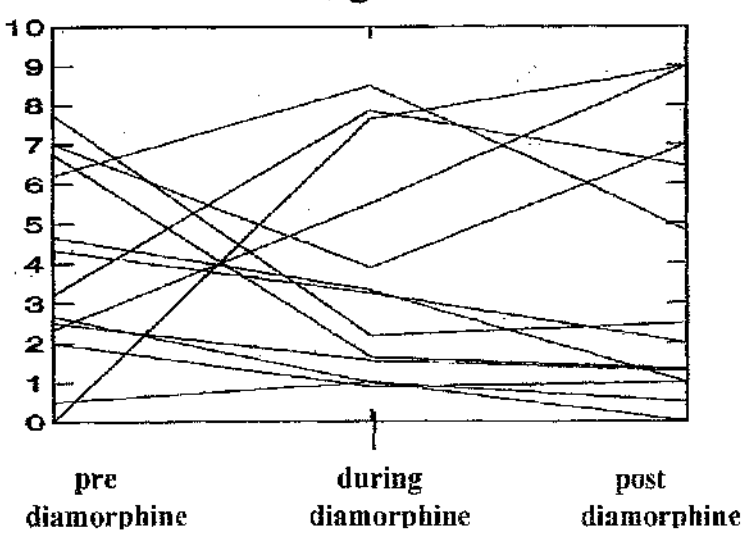


Fig III

Opioid Withdrawal Score



Appendix II

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Chapter 6 (Published Paper) Fallon M T, Hanks G W. Is morphine induced constipation dose related? Palliative Medicine 1999; 13: 357-361.

Abstract

Morphine, constipation and performance status in advanced cancer patients

Fifty patients with advanced cancer completed an observational study of constipation. Bowel function was assessed weekly for four weeks using a numerical scale measuring frequency of bowel movement, ease of passing stool and consistency of stool. Patients surviving were also assessed at six months. Thirty-five patients (70%) were constipated on referral to the palliative care service; of these, eight were not taking opioids. The proportion of constipated patients declined during the initial four weeks to 26%. Multiple regression analysis showed a highly significant correlation between persistent constipation at four weeks and deteriorating performance status, but no correlation between morphine dose and constipation. The relationship between morphine dose and laxative dose was examined specifically but no correlation was found. Of 12 patients surviving at six months, 10 were not constipated. Of these four were using oral morphine equivalent in daily doses of 40-5250mg but were not needing laxatives, nor other bowel interventions and six were not constipated but were needing a laxative in conjunction with oral morphine equivalent in doses of 20-3000mg/day.

Oral morphine invariably causes constipation when used in repeated dosage to treat cancer pain[1]. Other common unwanted effects such as sedation and nausea and vomiting are worse at the start of treatment with morphine but improve with continued use and often resolve completely[2]. In contrast it is commonly believed and taught that morphine-induced constipation does not get better with repeated administration. We have examined constipation associated with morphine in an observational study of patients with pain due to advanced cancer.

Patients, methods and results

Consecutive patients with advanced cancer referred to the Palliative Care Team who were judged clinically by a doctor on the team (MF) to have a prognosis of at least four weeks were included in the study whether or not they were receiving morphine. Laxatives were prescribed for all constipated patients or patients starting on morphine in accordance with a standard protocol (Appendix 1). This involves regular administration of a combination of a faecal softener and bowel stimulant, with appropriate dose titration according to response, and rectal measures as required. For the purpose of the study, patients were assessed by the same individual (MF) on referral, at weekly intervals for four weeks, and, for those surviving, at six months. For the first 4 weeks of the study the patients were seen daily for general review by a member of the palliative care team. Bowel function was assessed using a numerical scale designed specifically for this study, incorporating three items: frequency of bowel movements per week (based on the normal bowel habit (N) for each patient: 0=2<N, 1=N±1, 2=2>N), ease of passing stool (0=difficult, 1=normal, 2=easy) and consistency of stool (0=no stool, 1=hard, 2=normal, 3=loose). Normal function was defined as a total score of 4 or more, and constipation 3 or less. Performance status was measured using the ECOG scale (0 = normal activity, 4 = bedbound)[2]. A detailed record of laxative doses was kept and a note was made of concomitant medication.

Results

Fifty patients completed the study (24 males). They were aged 23 to 84 years and had a variety of primary cancers. On referral 35 patients (70%) were constipated; of these, eight were not taking opioid analgesics. The proportion of constipated patients declined during the initial four weeks to 26%. Factors contributing to persistent constipation in this group were examined at the end of the four week period.

Morphine dose, ECOG score, persistent constipation, and non-persistent constipation were examined in a multiple regression analysis. This showed a highly significant correlation between persistent constipation as

measured by the bowel function scores and deteriorating performance status (Figure I). All patients with persistent constipation had poor performance status (ECOG 3 or 4) and only 6% of patients with ECOG scores in this range *were not* constipated at four weeks. A comparison of ECOG scores in the persistent constipation group and the non-constipated group at four weeks demonstrated a highly significant difference ($p = 0.00001$).

There was no correlation between morphine dose and persistent constipation, nor between morphine dose and ECOG scores. The dose of laxatives was titrated for each patient according to response (not according to the dose of morphine). Patients with persistent constipation received the highest doses. Of the 50 patients, 14 were not receiving morphine, one was obstructed and one had an ileostomy and was not receiving laxatives. Of the other 34 patients, 30 were receiving laxatives containing danthron (either codanthramer or codanthrusate). Doses of danthron ranged from 50-1200mg/day. There was no correlation between the dose of morphine and the dose of danthron ($r = 0.234$ for the 30 patients receiving danthron; $r = 0.238$ if the whole group of 34 patients is included and an assumption is made that they did not need a danthron-containing laxative because they had only mild constipation. None of these four patients was constipated at four weeks).

At the six month follow up there were only 12 surviving patients. Four patients were not constipated, nor receiving laxatives in spite of using oral morphine equivalent daily doses of 40-5250mg; six patients were not constipated but were needing a laxative in conjunction with oral morphine in doses of 20-3000mg/day; only two patients had persistent constipation with morphine in spite of laxatives but of these one had a large pelvic tumour, and the other a cauda equina syndrome, sufficient in themselves to cause resistant constipation.

Comment

These data conflict with some long held beliefs about morphine-induced constipation. It seems clear that assiduous treatment with laxatives is effective in the majority of patients. There was no correlation between morphine dose and laxative dose. Persistent constipation in this patient population is more closely related to how ill and disabled the patient is (presumably associated with a poor dietary intake) than to their use of

morphine. We should be less reluctant to treat constipation aggressively in such patients given the misery associated with constipation. The suggestion that morphine-induced constipation is dose-dependent[3] is clearly not supported by our findings. Our long term data suggest that a proportion of patients may become tolerant to the constipating effects of morphine with repeated administration, and do not require continuing treatment with laxatives.

References

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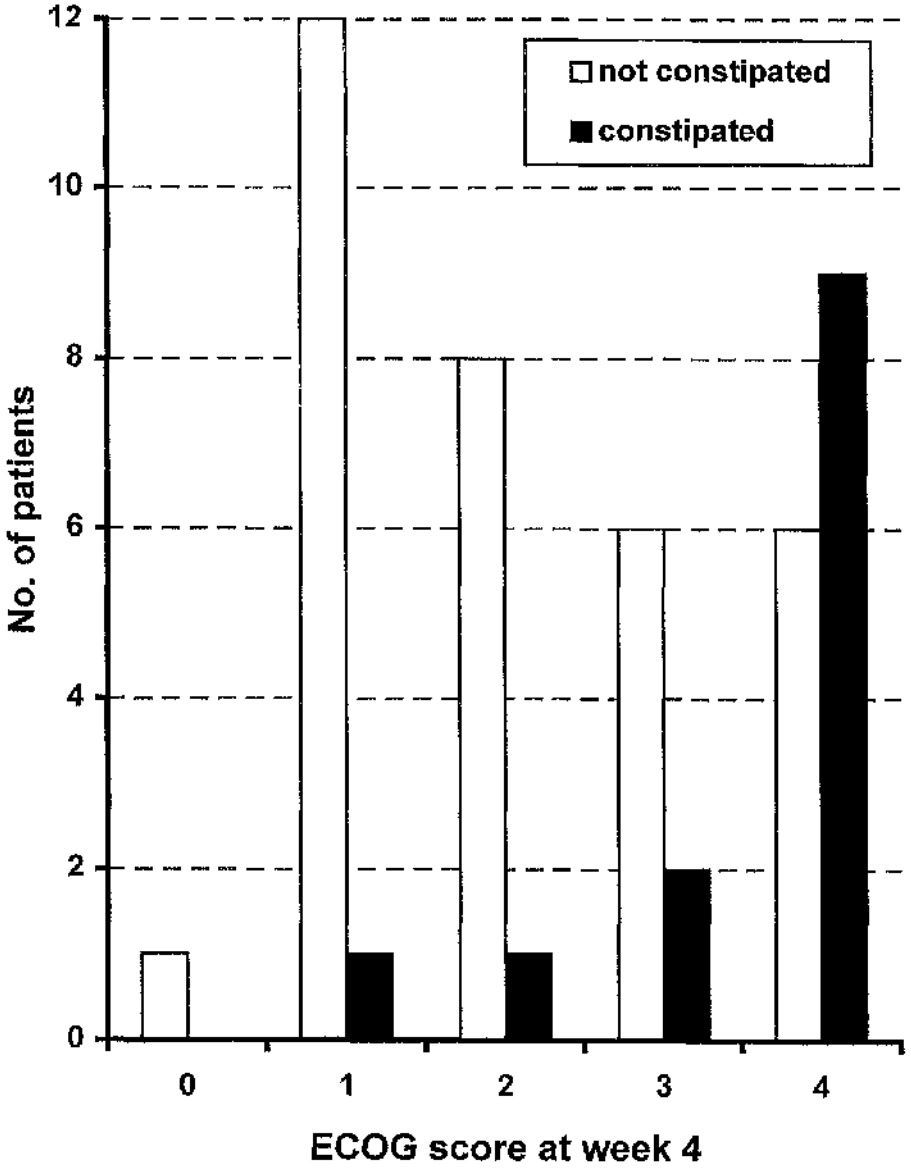
Figure 1

Relationship between resistant constipation and ECOG performance status in 50 consecutive cancer patients referred to a palliative care team (Fallon & Hanks)



Appendix 1

Protocol for management of constipation

1. All patients commencing opioid analgesia for moderate to severe pain should have a prophylactic laxative unless a contraindication exists. Laxative dose should usually be increased when opioid dose increases. Use a combination stimulant and softener - codanthrusate or codanthramer.

2. If the patient is already on a laxative which is acceptable, a change is not necessary and the dose should be increased when commencing or increasing opioids for moderate to severe pain.

3. Laxative dose should be titrated up until constipation is controlled.

4. If patient has persisting constipation on maximum dose of codanthrusate (3 tablets, 4 times a day) or codanthramer 20 mls q.i.d., then half the dose of laxative and add a small bowel flusher - lactulose 15 mls 3 times a day and increase as required, if tolerated.

5. If hard stool in rectum give glycerine and bisocodyl suppositories and increase the dose of oral laxative.

6. If soft stool in rectum give 2 bisocodyl suppositories (placed next to rectal mucosa) and increase the dose of stimulant laxative.

7. If patient has a spinal cord compression or cauda equina syndrome, give alternate day glycerine and bisocodyl suppositories and titrate oral laxative as required.

8. Enemata should be used if suppositories fail.

9. Any patient requiring enemata should be re-evaluated to assess reason for constipation and appropriate measures taken. This will invariably include an increase in laxative dose.

Chapter 7 (Published Paper) Fallon MT. European Journal of Pain 1999; 3 (supplement A) p.3-7

Constipation in cancer patients: prevalence, pathogenesis, relationship to opioids and cost-related issues.

Abstract

Among patients with advanced cancer, troublesome and persistent constipation is a more common symptom than pain. The major causes of constipation in cancer patients are inactivity, treatment with opioids, and poor fluid intake and nutrition. Opioids act to both decrease gut motility and decrease intestinal secretion and therefore harden the stool. Additional actiologies of constipation may be related to the cancer itself, general debility, concomitant diseases, or medication use. Analysis of results from a prospective, longitudinal follow-up study, has confirmed the high incidence of constipation among opioid-treated cancer patients and revealed that even optimal management of this symptom is only modestly successful in reducing constipation. This study also indicated that, in constipated cancer patients, bowel care entailed an average of 20 to 70 minutes per week of medical time and 55 to 120 minutes per week of nursing time, underscoring the high financial cost of this symptom to the health care system. According to another study, which involved 50 consecutive cancer patients referred to a palliative care unit, the development of resistant constipation was independent of morphine dose. However, this study revealed a highly statistically significant correlation between resistant constipation and patient functional status, which highlights the critical and often underestimated role of immobility in the development of constipation.

Introduction

Constipation is one of the most troublesome and persistent symptoms in patients with advanced cancer. Constipation can cause abdominal and rectal pain, and exacerbate vomiting and nausea. It is also a frequent cause of anorexia. Most cancer patients rank constipation as an even more common source of distress than pain. In addition to causing discomfort, constipation affects activities of daily living, nutritional intake, and socialization thus compromising quality of life. Recent exciting research into neurotransmitters involved in pain shows how complex constipation mechanisms may be.

Approximately 45% of hospice patients complain of constipation on admission (St Christophers Hospice, 1986). Laxative treatment is necessary in about 87% of patients who are receiving a strong opioid analgesic (Sykes, 1997). Even among cancer patients who are not being treated with strong opioids, as many as 63% may require a laxative (Sykes, 1997). Moreover, despite our best efforts, rectal laxatives will be needed in up to 40% of hospice patients, depending on the population (Twycross and Lack, 1986).

After a review of the most common causes and underlying mechanisms of constipation in cancer patients, this article will describe the findings of a study that investigated the clinical course and pharmacoeconomics of this symptom in opioid-treated cancer patients. The relationship of constipation to morphine dose and patient performance status is also discussed.

Causes of Constipation in Cancer Patients

The actiology of constipation in patients with cancer is multifactorial. The chief culprits include immobility, opioid analgesics, inadequate fluid intake and poor nutrition. Other contributing factors may be related to the cancer itself, such as hypercalcaemia, obstruction from an intra-abdominal tumour, spinal cord compression with loss of rectal sensation, cauda equina syndrome with abolition of the anocolonic reflex, and depression. Alternatively, the causes of constipation may reflect the presence of concomitant disorders such as hemorrhoids, anal fissure, or endocrine dysfunction. In addition to opioids, medications such as antiemetics, drugs with anticholinergic action, aluminium salts, or nonsteroidal anti-inflammatory agents may also be implicated. The roles of weakness, confusion, and difficulty in reaching the toilet should not be overlooked (Fallon and Hanks, 1994).

Exogenous opioids are well known to constipate, not by relaxing intestinal muscle but by suppressing forward peristalsis and raising sphincter pressure. These effects are apparent in both the small and the large intestine.

Animal research has revealed multiple putative transmitter peptides and amines in myenteric neurones. Acetylcholine and vasoactive intestinal peptide (VIP) are the principle neurotransmitters involved in the control of peristalsis. Anticholinergic agents will obviously induce constipation, however both acetylcholine and VIP neurones are modulated by other agents.

Opioid receptors are present on gut smooth muscle cells and on all levels of intestinal afferent neurons. Gut opioid effects involve both central and peripheral receptors in animals, whereas only a peripheral opioid contribution has been confirmed in humans (Sykes, 1997). Moreover, in humans parenterally administered morphine has been shown to slow gut transit and reduce stool frequency (Kaufman et al., 1988). It is generally accepted that opioid receptors in the gut wall can be reached via the systemic circulation, as well as via the gut lumen.

Constipation-inducing effects of opioids include an increase in the tone of the ileocecal valve and a reduction in the peristaltic component of motility in the small intestine and colon. Opioids impair the defaecation reflex by reducing sensitivity to rectal distension and by increasing the tone of the internal anal sphincter. Increased electrolyte and water absorption in the small intestine and colon has been observed during induced diarrhoea in the experimental setting. Fluid absorption in the gut is dependent on electrogenic sodium transport that is mediated by the sodium/potassium-ATPase system. At the mucosal surface, the cyclic AMP-dependent system that mediates chloride transport and consequently, fluid secretion, is a crucial part of the overall process of fluid absorption and secretion. Evidence from experimental animal studies has definitively shown that electrolyte and water transport, which is under neuronal control, is affected by opioids (Plonowski et al., 1997; Turvill and Farthing, 1997).

Recent research has helped to elucidate the relationship between cancer-associated pain and psychological stress and alterations in bowel habit. Tachykinins and tachykinin receptor expression have been implicated in disturbances of gut motility caused by stress and pain. Tachykinins affect the intestinal muscle and enteric nerves and cause sensitization or stimulation of primary afferent nerve fibers. These actions not uncommonly lead to hypomotility, as has been demonstrated in cases of postoperative gut ileus. Central neurokinin$_1$ (NK_1) receptors are also involved in pain-related shutdown

of gastrointestinal motility. This is a fascinating area for future research; substance P, neurokinins, and other tachykinins have attracted much interest in the examination of the plasticity of the central nervous system pain pathways. Perhaps we should also be examining such plasticity mechanisms of constipation.

Clinical Course and Pharmacoeconomics of Constipation

A prospective, longitudinal follow-up study has been conducted to examine the clinical course of constipation in community-based cancer patients with a life expectancy of at least one month who were receiving strong opioids. The study excluded patients with a primary bowel malignancy or a stoma.

Five men and 11 women who met these criteria were enrolled in the study. These 16 patients ranged in age from 40 to 78 years (median, 63 years). The primary diagnosis was breast carcinoma in six patients, bronchial carcinoma in three patients, and other malignancies in seven patients. The duration of opioid use spanned one week to two years, with a median of 38 weeks. At entry into the study, 14 patients were already taking laxatives and 10 of these remained constipated despite laxative treatment.

A critical aspect of the study was the measurement of the constipation score. This score assesses the frequency and severity of constipation by quantitating the number of times the bowels opened in the last week, the ease of passing stool, and the consistency of stool passed (Table 1). The median bowel status score in this group of patients was 2.5 (range, 1 to 4) out of a possible total score of 7, where a score of 3 or less is considered to be significant constipation.

Eastern Cooperative Oncology Group (ECOG) scores were used to evaluate functional status in these patients. An ECOG score of 0 represents normal activity, a score of 1 indicates that the patient has symptoms but is nearly fully ambulatory, 2 means that the patient is in bed for less than half of normal daytime hours, 3 means that the patient is in bed for more than half of normal daytime hours, and 4 refers to a complete inability to get out of bed. In this population ECOG scores for the first four weeks of the study ranged from 0 to 2, with a median of 1.5. The effect of constipation on patients' lives

ranged from 0 to 3 (median, 1.25), where 0 indicates no effect at all and 3 represents a very significant effect. The spectrum of typical symptoms associated with constipation is illustrated in Table 2, which shows a scatter of prevalence throughout the first four weeks of the study.

Patients kept daily diaries in which they recorded how much time was spent each week talking with a hospital physician, general practitioner, or nurse about bowel care. Analysis of these diaries revealed that the major costs associated with constipation are not the costs of laxatives, suppositories, and enemata but rather, the costs of medical and nursing time and possible hospital and hospice admissions as a result of constipation. Bowel care entailed an average of 20 to 70 minutes per week of medical time and 55 to 120 minutes per week of nursing time. Despite best efforts to optimize laxative prescription and maximize mobility, one to two study participants still required enemata each week.

The outcome of the study revealed that even optimal management of constipation with careful follow-up is only modestly successful. After modification of laxative prescriptions, eight patients reported an improvement in constipation and six patients experienced no change. One patient remained constipated with no obvious symptoms and took no laxatives and the other patient deceased after two weeks of study.

It is evident that some patients develop tolerance to the constipating side-effect of opioids while others remain constipated despite best efforts to reverse this symptom. The relationship between resistant constipation and lack of tolerance to this opioid effect is not so clear.

Relationship between constipation, opioid dose, and functional status

We studied 50 consecutive cancer patients referred to the palliative care team in an attempt to determine the incidence of persistent constipation despite best efforts and to identify those clinical characteristics most strongly associated with resistant constipation (Fallon & Hanks, Chapter 6). The study population included 26 women and 24 men ranging in age from 23 to 84 years. All patients with constipation and all patients starting on morphine were treated with a faecal softener and a bowel

stimulant and, when required, with rectal measures. Laxative doses were titrated according to clinical response.

Bowel function was assessed at the time of referral, weekly for four weeks and, in surviving patients, at six months using the constipation score described above. Detailed records of laxative doses and concomitant medications were kept. Overall, 70% of the total population were constipated at the start of the study. Over the course of four weeks, this proportion decreased to 26%. The prevalence of constipation according to morphine dose at referral, weeks one to three, and week four is shown in Table 3. Multivariate regression analysis failed to detect any correlation between morphine dose and resistant constipation, as defined by a constipation score ≤ 3 or constipation requiring regular enemata in the absence of an obvious cause such as spinal cord compression. There was also no relationship between morphine dose and laxative dose.

In contrast, there was a highly significant correlation between resistant constipation and ECOG performance status. As illustrated in Figure 1, the highest incidence of resistant constipation was observed among bed-bound patients with the highest ECOG score of 4. This suggests that the more mobile the patient, the easier it is to resolve constipation and that, conversely, the less mobile the patient, the more resistant the constipation is to treatment.

Conclusions

Persistent constipation may be a source of great distress to cancer patients and their caregivers. In addition to the personal cost, it is now recognized that the financial cost of constipation to the health care system is high because this symptom is so time-consuming for medical and nursing staff. It is clear that the management of constipation must be multifaceted and that even optimal prescription of laxatives is not always the solution. It is of particular note that the study described here shows poor mobility of patients, rather than the magnitude of the opioid dose, as a cause of constipation. The indicators are pointing towards the fact that resistant constipation is complex and much more than lack of tolerance to this opioid side-effect. In the future, new agents that antagonize tachykinin receptors, such as NK_1 receptors, may emerge as an innovative approach to this challenging problem.

Constipation is not just multifactorial in aetiology, but may emerge as the complex outcome of disturbances at neurotransmitter level as well.

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Table 1

Constipation Score

Total Constipation Score; Maximum Score is 7 (3 or less = constipation)

☐ Number of times bowels opened in the last week (0-2)

0	>2 times fewer than normal
1	normal ± 1
2	>2 times more than normal

☐ Ease of passing stool (0-2)

0	difficult
1	normal
2	easy

☐ Consistency of stool (0-3)

0	no stool
1	hard stool
2	normal stool
3	loose stool

Table 2

Symptoms of constipation in 16 opioid-treated cancer patients participating in a multicentre, prospective, longitudinal follow-up study

Number of patients experiencing symptom				
Symptom	**Week 1**	**Week 2**	**Week 3**	**Week 4**
Pain passing stool	1	1	0	0
Nausea	3	1	0	0
Anorexia	0	1	2	0
Flatulence	2	0	0	0
Abdominal pain	1	2	0	1
Malaise	1	0	1	1
Haemorrhoids	0	1	2	2

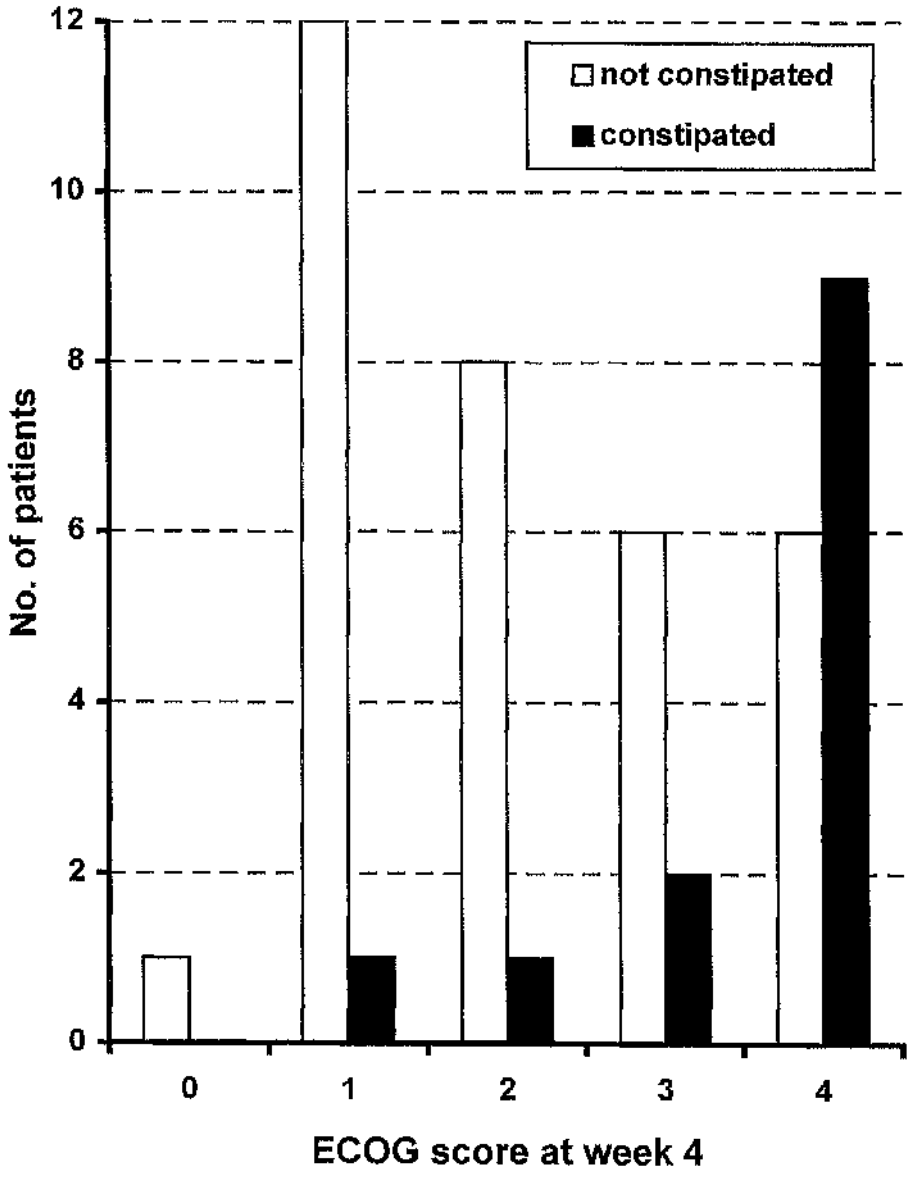
Table 3

Prevalence of constipation according to morphine dose among 50 consecutive cancer patients referred to a palliative care team (Fallon & Hanks)

Number of patients constipated				
Morphine dose	**Total number of patients**	**Time of referral**	**Weeks 1 to 3**	**Week 4**
0	14	8 (57%)	5 (36%)	0
≤ 200 mg/day	26	21 (81%)	19 (75%)	9 (35%)
201 to 1200 mg/day	4	2 (50%)	3 (75%)	2 (50%)
> 1200 mg/day	6	4 (67%)	3 (50%)	2 (33%)
All dose levels	50	35 (70%)	30 (60%)	13 (26%)

Figure 1

Relationship between resistant constipation and ECOG performance status in 50 consecutive cancer patients referred to a palliative care team (Fallon & Hanks)



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The role of ketamine in pain control

Ketamine has been used for 30 years as a dissociative general anaesthetic. Ketamine activates the limbic system and depresses the cerebral cortex, producing profound analgesia, slight respiratory depression, cardiovascular stimulation and amnesia. The protective reflexes are maintained.

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist. NMDA receptors are glutamate receptors, glutamate having been long recognised as an important transmitter. It is the main excitatory transmitter in the central nervous system (CNS).

There has been intense interest in the role of ketamine as an analgesic in recent years, but its mechanism of action and appropriate use are not fully understood. We need to logically and systematically examine our approach to its current use as an analgesic and its future evaluation in clinical trials.

Transmission of pain

Glutamate is important in the peripheral nociceptive sensory fibres and in the ascending neurones, which convey messages to the thalamus and beyond. Glutamate is, of course, present in a 'soup' of neurotransmitters. The balance between these neurotransmitters is constantly fluctuating, hence their dynamic role in pain response and in the plasticity of the CNS.

In addition to the changes in neurotransmitters, evidence suggests that the roles of receptors evolve over time. This applies to opioid and non-opioid receptors. An example of the latter is the initial activation of AMPA (alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) receptors in the dorsal horn. It is only after AMPA receptor activation that the NMDA receptors are activated, with the

consequent conversion of a small to large amplitude response and a corresponding increase in pain intensity. This will be discussed later as the 'wind-up' phenomenon.

These are just some of the complexities that occur in the central nervous system, resulting in neural plasticity. Pain is dynamic, in terms of process and outcome. The role of NMDA antagonists, such as ketamine, in influencing the dynamic modification of the nervous system in response to injury has been shown experimentally in animals at spinal cord and cortical levels.

Experimental evidence

Animal models of neuropathic pain have helped us to analyse the basic underlying pathophysiological mechanisms in difficult pain syndromes such as neuropathic pain.[1,2] Among the phenomena observed are spontaneous activity of primary afferent neurones and electrophysiological hyperactivity of the dorsal horn and spinothalamic tract, altered regional spinal cord metabolism and other CNS abnormalities.[3-7] These dorsal horn abnormalities may be the result of the neuronal hyperactivity mediated by NMDA receptors and agonists.[8,9] In phantom limb pain, somatosensory input of sufficient intensity and duration may produce lasting changes in central neural structures and, therefore, preamputation (pain) experience has a critical role in the genesis of phantom limb pain [10,11] This is thought to be mediated via NMDA receptors.

Key points

- Animal experimental evidence and clinical evidence suggest that NMDA antagonists such as ketamine can have a useful analgesic role.
- The analgesic role of ketamine seems to be linked to an alteration in opioid sensitivity.
- The physiological process of 'wind-up' correlates with the clinical features of allodynia, hyperalgesia, and prolongation of evoked pain response.

- Those patients with the above triad are most likely to have an analgesic response. Other elements of pain will not necessarily improve.

- Care should be taken with opioid doses when ketamine is introduced: a decrease in the former may be necessary.

Ischaemia-induced hyperalgesia is abolished by direct intrathecal application of NMDA receptor antagonists in small volumes. Work on rats suggests that the action in the spinal cord is local.[12]

In inflammation, NMDA receptor activation induces the enhanced pain state.[13]

Clinical role and experimental knowledge

There is substantial evidence that NMDA receptors are involved in the induction and maintenance of the pain response in:

- wind-up phenomenon
- peripheral inflammation
- peripheral neuropathy
- peripheral nerve section
- spinal ischaemia
- spinal disinhibition
- peripheral ischaemia

The clinical correlates are:

- any pain syndrome with allodynia, hyperalgesia and prolongation of pain response
- inflammatory pain
- neuropathic pain syndrome
- phantom limb pain
- peripheral vascular disease pain

An essential part of the future place of ketamine in analgesia is to analyse our current animal experimental knowledge and, with the clinical data accrued so far, to formulate an acceptable strategy for its use in pain management. This immediately brings us to the wind-up phenomenon. This is mediated by the activation of the NMDA receptor, whereby the C-fibre-induced activity of dorsal horn nociceptive neurones is enhanced and prolonged.

Activation of C-fibres can result in a substantial and prolonged increase in the flexion withdrawal reflex in rats. This was the first evidence for the existence of central hypersensitivity in pain states, now known to be NMDA receptor-mediated.[14]

The wind-up phenomenon has been demonstrated in animals and humans. [15,16] The NMDA receptor is not believed to mediate the initial acute responses to pain: these are transmitted via the AMPA glutamate receptor. This is when the soup of transmitters in a dynamic pain process interacts with modifying receptors to cause functional alterations in central transmission processes, resulting in the clinical phenomena that accompany wind-up.

When the AMPA receptor continues to be stimulated and conditions are right, co-operation between the peptides and glutamate released in response to a painful stimulus allow the NMDA receptor to be activated. The NMDA receptor then has a crucial role in the maintenance of prolonged pain states. It mediates dramatic increases in the duration and the magnitude of cell responses while the input into the spinal cord remains constant.

This phenomenon converts simple touch input into the painful sensation to touch we call allodynia. It also means that a painful response to any given painful stimulus is magnified (hyperalgesia) and prolonged. While wind-up is a process of C-fibres, the central sensitisation that develops means that incoming A-fibre inputs are also amplified.

All these phenomena are sensitive to NMDA receptor antagonists that have been applied intrathecally or systemically.[15]

Clinical assessment for ketamine use

Clinically, we can identify the triad of allodynia, hyperalgesia, and prolongation of pain response in a variety of pathophysiological processes. Sometimes the complete triad is not present, although some elements are obvious. It is important to acknowledge that these phenomena may coexist with other pain expressions, as we commonly find in the complex mixed pains in cancer pain.

As with the management of any symptoms, an accurate clinical assessment is critical to successful treatment. NMDA antagonists, such as ketamine, are not the answer to all pains that are difficult to control with the standard WHO analgesic guidelines.[17] This kind of indiscriminate use would only hamper further understanding and evaluation of ketamine and cause patients unacceptable side-effects.

We have sufficient experimental and clinical knowledge to select patients who have a good chance of a clinical response to ketamine. Patients in neuropathic, inflammatory, ischaemic and phantom limb pain groups and those who have the clinical triad of allodynia, hyperalgesia and hyperpathia which is prolongation of pain response, are most likely to have a favourable analgesic response to ketamine. They may achieve relief of the symptoms mediated via the NMDA receptors but still have pain mediated via other pathways.

Side effects of ketamine

Sensory information in the brain is processed via NMDA receptor-mediated transmission. It is therefore expected that NMDA antagonists will produce several side-effects. The following have been described with anaesthetic and subanaesthetic doses used in analgesia:

- Confusion

- Delirium
- Vivid dreams
- Hallucinations
- Feelings of detachment from the body

In our experience the adjective most frequently used by patients is 'strange'.

Some clinicians routinely administer haloperidol or a benzodiazepine, such as midazolam or lorazepam, with ketamine. The rationale for using haloperidol is that it binds to central sigma receptors that are thought to mediate the excitatory effects of ketamine at higher doses.

Overuse of haloperidol or benzodiazepines is likely as several of the symptoms prompting their use could be due to opioid toxicity. Animal experiments and clinical studies have shown that NMDA antagonists alter the response to opioids.[19, 20] Furthermore, benzodiazepines increase the bioavailability of ketamine by inhibition of hepatic metabolism. Explanations of potential side-effects are important and help to decrease anxiety if these side-effects do occur.

Ketamine and opioids

The main action of opioids is on receptors at C-fibre terminals: release of multiple transmitters from these terminals is affected and this explains why opioids are such good analgesics.

There is substantial animal experimental evidence to show that NMDA antagonists attenuate as well as reverse morphine tolerance, [19, 21, 22] This correlates with the clinical phenomenon of appearance or reappearance of opioid sensitivity, which can be seen after treatment with ketamine begins. This improved response to opioids may lead to increased opioid side-effects if the dose is not adjusted appropriately.

Opioid tolerance - or a shift in the opioid dose-analgesic response curve to the right - is a complex area and the role of NMDA receptor activation will remain of great interest to researchers. It is another example of the great plasticity of the CNS. Some reports indicate that ketamine binds stereospecifically to opioid receptors in the brain and spinal cord and that naloxone reverses the effect of ketamine. [23-25] Naloxone might reverse the increase in opioid responsiveness in this situation.

It has been observed that hyperalgesia and morphine tolerance may be related by common neural substrates that interact at the level of excitatory amino acid receptor activation and related intracellular events.[26]

Lack of response to opioid analgesics is often associated with neuropathic pain, but this whole area has become confused. First, the term 'opioid poorly responsive' pain is preferable to describe this lack of response.[27] This should be a clinical diagnosis made retrospectively after an adequate trial of opioids. In animal studies, loss or dysfunction of presynaptic opioid receptors can be overcome by increasing the dose of opioid.[28] In pain, where the NMDA receptor is operating and there is reduced opioid sensitivity, this, too, can be overcome by dose escalation.[29] Therefore, relative lack of opioid response is a function of many factors, including unacceptable side-effects of opioid dose escalation.

Any element of pain responding poorly to opioids that can be addressed is important: there is animal evidence for NMDA receptor activation in this type of pain, so it makes sense to look at NMDA antagonists.

Clinical Use

In the clinic we are sometimes faced with the situation of inadequate analgesia despite an appropriate trial of opioid analgesia (usually morphine) and use of appropriate adjuvant analgesics. This is particularly common in neuropathic and some inflammatory pains associated with malignancy. Such situations can be associated with much distress, making any movement, toileting, washing, and even communicating very difficult.

Given the significant in vitro and animal in vivo experimental evidence in addition to numerous case reports, for the use of NMDA antagonists in certain pain states a protocol (developed by Marie Fallon in Bristol) for the use of ketamine in patients with uncontrolled pain due to malignancy was put in place (1993 - 1995). Patients who fulfilled the following criteria were approached to give informed consent for a therapeutic trial of analgesic doses of ketamine.

1. Alert, orientated
2. Able to give informed consent
3. Patient had an adequate trial of opioid analgesia titrated against pain
4. Patient had an adequate trial of adjuvant analgesia.
5. Patient not showing any signs of opioid toxicity e.g. hallucinations, vivid dreams
6. Diagnosis of pain syndrome is neuropathic and/or inflammatory and/or ischaemic
7. Clinical features must include two of the following three phenomena:

   hyperalgesia

   hyperpathia

   allodynia
8. Opioid dose is reduced by 25% on day 1 of ketamine and adjusted accordingly. (For caution).
9. Ketamine is delivered by continuous subcutaneous infusion at a starting dose of 0.1mg/kg/hour and increasing if necessary by 0.1 mg/kg/day every 24 hours up to a maximum of 0.6 mg/kg/day.
10. Clinical response is noted daily in terms of:

    i) pain - none, mild, moderate, severe

    ii) presence of hyperalgesia Yes/No

    hyperpathia Yes/No

    allodynia Yes/No

    iii) ketamine dose

iv)	opioid dose		
v)	adverse effects:	drowsiness	Yes/No
		hallucinations	Yes/No
		vivid dreams	Yes/No
		mycolonic jerks	Yes/No
		confusion	Yes/No

Table 1 (see overleaf) is a summary of the last seven patients in Bristol in whom ketamine has been used. A good response often meant that toileting, bathing and cleansing of skin and wounds became possible with associated improvement in overall affect and quality of life.

Interestingly, those patients with a partial response (four out of seven patients) required the same amount of opioid, while three out of seven patients who experienced a substantial beneficial effect from ketamine all decreased their opioid dose. The range of decrease was between 2,000 mg and 60 mg (mean 200 mg) of oral morphine equivalent in 24 hours. It is difficult to say if this is a reflection of improved analgesia due to ketamine alone, an increased response to opioids or a combination of both.

Dextromethorphan is also used as an antagonist at this site and is used to treat cough in the clinical setting.

Conclusion

There is good experimental and clinical evidence for the use of the NMDA antagonist ketamine in specific circumstances. Ketamine acts by blocking the wind-up phenomenon that happens at the NMDA receptor sites, therefore resetting the pain transmission pathway. Clinically, this is manifest as blocking allodynia, hyperalgesia and prolongation of the pain response.

Table 1: Seven cases treated with ketamine

Case Number	Age	Sex	Diagnosis	Indications	Ketamine Dose/24 hr	Opioid	Response
1	42	F	Cervical cancer	Neuropathic pain, allodynia, hyperalgesia	300 mg	↓ 20%	++
2	72	F	Vulval cancer	Inflamed tumour, allodynia, hyperalgesia, hyperpathia	500 mg	↓ morphine discontinued	++
3	73	F	Bronchial cancer	Brachial plexopathy, allodynia	300 mg	→	+
4	78	M	Rectal cancer, ischaemic foot	Allodynia, hyperalgesia of ischaemic foot	300 mg	↓ 30%	++ 5
5	82	F	Wegener's granulomatosis	Superinfected, ulcerated lesion, allodynia, hyperalgesia	200 mg	→	+
6	63	F	Rectal cancer	Phantom anus pain syndrome, allodynia, hyperalgesia	200 mg	→	+
7	43	F	Lung cancer	Neuropathic pain, allodynia, hyperalgesia, hyperpathia	200 mg	→	+

Response: ++ marked effect + partial effect. Opioid dose: ↓ decreased, → unchanged.

Where this triad is present, particularly in the presence of neuropathic, inflammatory or vascular aetiology, ketamine is strongly indicated if the application of the standard WHO analgesic guidelines has already been applied.

Care is required with the opioid dose when ketamine is introduced. Sustained-release opioid preparations should be substituted with immediate-release formulas and an opioid dose reduction should be considered in patients starting a regimen of ketamine for analgesic purposes. The basis for this is the clear pre-clinical evidence of an enhanced morphine response when ketamine is added and the clinical experience to date with our protocol which backs up the pre-clinical data.

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Chapter 9

Opioid rotation: Does it have a role? – (Published Paper) Fallon M T. Palliative Medicine, 1998; 12: 61-62.

Opioid rotation is the term given to a switch in opioids. The aim is to achieve a better balance between analgesia and side-effects. The keystone to the rationale behind opioid rotation is incomplete cross-tolerance.

Tolerance is the phenomenon whereby the dose of a drug needs to be increased to achieve the same effect. It is also described as a shift to the right in the dose response curve. Selective tolerance describes stable analgesia accompanied by diminution of side-effects.

Tolerance is a complex phenomenon and there has been some controversy as to how often it occurs with systemic opioids in the clinical management of cancer pain[1]. While tolerance occurs to adverse effects of opioids, clinically relevant tolerance to the analgesic effects is thought to be uncommon.

Cross-tolerance describes the phenomenon of tolerance to one drug resulting in tolerance to another drug. Incomplete cross-tolerance may apply to wanted effects e.g. analgesia, and unwanted effects e.g. sedation, nausea, vomiting, dry mouth and constipation.

The benefit of a switch from one opioid to another opioid depends on cross-tolerance to the analgesic effects being less than cross-tolerance to the adverse effects.

There is clinical evidence that cross-tolerance occurs; the patient with prior exposure to opioids is less susceptible to significant opioid-initiation adverse effects. Incomplete cross-tolerance is evidenced in the patient who has a recurrence of the initiation side-effects of opioids after switching opioids. Subclinical or even clinical opioid withdrawal symptoms on switching from one opioid to another opioid also reflects incomplete cross-tolerance. At a cellular level the theories of incomplete cross-

tolerance are complex but include binding to different receptor subtypes and the use of different secondary messenger systems by different opioids.

The clinical advantage of opioid rotation lies in the possibility of incomplete cross-tolerance favouring analgesia more than adverse effects. The disadvantage is that the clinician cannot know in advance if an opioid switch will increase analgesia more than adverse effects. In addition, the equianalgesic dose of the alternative opioid chosen may be uncertain: it will depend on the opioids being used, the individual patient, a degree of cross-tolerance, as well as the nature of the pain. The patient in the higher dose range is potentially at greater risk of the equianalgesic dose being several-fold different than expected.

Evidence that tables of equianalgesic dose conversions differ from the clinical situation in opioid rotation comes from clinical observations [2,3]. Methadone has been used in opioid rotation, particularly in North America. A further complication of a methadone switch is the emerging NMDA (N-methyl-D-aspartate) antagonist activity.

Consideration of the place of opioid rotation in the management of cancer pain naturally leads to the concept of opioid responsiveness. One of the commonest reasons for switching opioids is poorly controlled pain with unacceptable adverse affects from the current opioid. It is believed that opioid responsiveness should not be judged on the analgesic response to one opioid and should only be assessed after a trial of at least one alternative opioid.[5]

To avoid unnecessary complication in the management of cancer pain it is important to examine some basic clinical facts. Morphine appears to have no clinically relevant ceiling effect to analgesia; hence there is no specific point of pain relief or inadequate pain relief with morphine but a point when adverse effects mean further titration of morphine is not possible. Whether unacceptable adverse effects occur before adequate analgesia is achieved depends on patient, drug and pain-related factors. The anxious patient who uses morphine as an anxiolytic is likely to reach unacceptable adverse effects

before adequate analgesia. Similarly the inexpert use of morphine, with inappropriately rapid titration, lack of attention to prevention and management of adverse effects and inadequate use of adjuvant analgesics will result in unacceptable adverse effects before adequate analgesia is reached.

Some pains are less responsive to opioids than others. Neuropathic pain is commonly quoted as being opioid poorly-responsive. There is substantial animal experimental evidence that neuropathic pain can be controlled by opioids. However in the clinical situation large doses are often required and adverse effects may become unacceptable before analgesia is reached rather than there being not any predetermined absence of opioid-responsiveness. Opioid responsiveness is therefore a continuum which depends on several factors[4].

It is of some concern that several of the reports in the literature advocating opioid rotation, have done so on the basis of pain in the confused, agitated, and evidently opioid-toxic patient. A less complicated and more predictable approach would be to:

- review the clinical situation and pain syndrome
- review adjuvant analgesics
- decrease the opioid dose avoiding sustained release preparations
- deal with the altered sensorium secondary to opioid toxicity; using haloperidol or other drugs
- correct any contributing abnormal biochemistry; opioid toxic patients simply do not drink enough

At present none of the other strong opioid analgesics has been shown to have advantages which would make it preferable to morphine for routine use. However there is evidence that a failure to respond to one opioid does not mean failure to respond to all opioids and an opioid switch may allow pain control to be achieved without disabling side-effects[5].

The most frequently used alternative opioids are fentanyl, methadone and phenazocine. Oxycodone and hydromorphone will be future alternatives. Methadone is a difficult drug to use for the non-specialist. Titration can be difficult and equianalgesic conversion can be complex. Fentanyl is an

interesting drug and more precise information is awaited from clinical trials, however it is not suitable in the unstable pain syndrome. Phenazocine is a useful alternative to morphine, particularly if dysphoria exists. It is important to remember that some of the alternatives to morphine are much more potent than morphine.

An active quest for safe, more efficient analgesia, with a better balance between analgesia and unwanted effects is our universal aim. Opioids, of which morphine is the most commonly used, are the mainstay of moderate to severe cancer pain management. Opioid responsiveness is a continuum which can be affected by many factors, but inappropriate assessment and prescribing can shift a patient to the less responsive end of the continuum. Basic reassessment should be a prerequisite before any thought is given to opioid rotation.

Opioid responsiveness should not always be based on one opioid and in some situations an opioid switch can result in a better balance between wanted and unwanted effects because of incomplete cross-tolerance. Opioid rotation will have a place in the management of a selected group of patients. We need to examine the pharmacodynamic effects of the different opioids in the clinical setting, but at present this information is lacking.

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Chapter 10

Attenuation of morphine tolerance by an N-methyl-D-aspartate receptor antagonist

It is traditionally taught that pharmacological tolerance to morphine is not a clinically relevant phenomenon in cancer pain management. This has been one of the main themes of this thesis. Studies of opioid use in patients with pain demonstrate that changes in the pain stimulus, associated with progression of tumour in cancer pain patients, is the most common cause of dose escalation.[1] While physician concern that the development of analgesic tolerance limits the chronic use of opioids is not validated in clinical studies in cancer pain patients, the phenomenon of a specific type of opioid tolerance is of practical concern in the care of a subgroup of patients. This group have the clinical correlates of central wind up.

Tolerance is a complex phenomenon made up of many mechanisms. The role of each mechanism will vary in each situation. Some of the clinical endpoints are discussed in the accompanying editorial, 'Opioid rotation: does it have a role?' Chapter 9. However, one mechanism of particular interest in morphine tolerance is the N-methyl-D-aspartate (NMDA) mechanism.

Recent studies have demonstrated that the excitatory amino acid (EAA) receptor system is involved in morphine tolerance and dependence.[2-4] Since the 1980's, EAAs, including glutamate and aspartate, have been identified as neurotransmitters in the vertebrate central nervous system (CNS). An important aspect of the NMDA subtype of EAA receptor is that it opens a distinctive membrane channel, characterised by voltage-dependent Mg^{2+} blockade and high permeability to calcium ions.[5] Physiological increases in intracellular calcium subsequent to receptor activation can initiate several metabolic changes in the cell.[5-6] NMDA antagonists including MK801, LY274614, dextromethorphan, and ketamine can attenuate or reverse the development of tolerance to morphine's analgesic effects.[2, 3] It is interesting that the attenuation of morphine tolerance by LY274614 is dose dependent.[7] Also, animals tested one week after the discontinuation of drug treatments (LY274614 plus morphine) retained their sensitivity to morphine analgesia whereas control animals (morphine only) remained

relatively tolerant.[4, 7] Interestingly the ability of LY274614 to affect the development of tolerance and the subsequent sensitivity of animals to morphine requires co-administration of LY274614 when morphine is present and therefore occupying opioid receptors.

In contrast to MK801 or LY274614, ketamine is available for clinical drug use. It is a non-competitive NMDA receptor antagonist. Ketamine is structurally related to phencyclidine (PCP) and like other PCP-like drugs it has anaesthetic, antinociceptive, psychotomimetic, anticonvulsant, neuroprotective and amnesic effects.[8] Animal studies show ketamine to attenuate morphine tolerance.[9]

Ketamine used in subanaesthetic doses has analgesic effects in humans.[10-12] The main side effect at subanaesthetic doses are psychotomimetic effects which are usually dose-related.[13] There is animal evidence to suggest that NMDA receptors are required for both the induction and maintenance of morphine tolerance.[4] The same animal work is consistent with induction and maintenance of tolerance involving a time lag consistent with cellular biosynthetic processes.

Central sensitisation of the spinal cord projection neurones may be modulated by the release of EAA's, especially glutamate, and the subsequent activation of the NMDA receptor. These neuronal changes may be attenuated experimentally with NMDA receptor antagonists.[14]

Interestingly the development of tolerance to morphine's analgesic effects can also be attenuated by co-administration of nitric oxide synthesis (NOS) inhibitors.[15] The NOS inhibitors, just like the NMDA receptor antagonists, can reverse morphine tolerance.[15]

Studies to investigate the relationship between NMDA - mediated events and opioid receptor events have linked mu receptor occupancy by morphine to protein kinase C activation of NMDA receptors, which results in a Ca^{++} influx and the formation of nitric oxide. These changes can then result in longer lasting changes of gene expression that are the basis of persistent tolerance and dependence.[16] Recent work in mice has shown that the both competitive and non-competitive NMDA receptor antagonists block the development of anti-nociceptive tolerance to morphine, but not of that to fentanyl

nor to a delta selective agonist.[17] This would suggest that there may be significant mechanistic differences between the development of tolerance to morphine (with affinity at mu, delta and kappa receptors) and more selective mu agonists. This would mean that inhibition of the development of opioid tolerance by NMDA antagonists does not happen with all opioids, but is selective for tolerance induced by morphine. The other interesting phenomenon is the effect of duration of pain on tolerance to morphine. This relates to gene induction, the changing soup of neurotransmitters and plasticity of the central nervous system.

Ketamine is widely used to control nociceptive pain in intensive care and emergency settings.[16, 19] Ketamine has also been used in the management of patients with cancer related and non-malignant chronic pain syndromes.[20] However the work reported to date consists of small numbers of case reports or more recently small randomised controlled trials in non-malignant pain.[21] This work attempts to clarify the role of ketamine. All animal experimental work in this area clearly demonstrates that it is a combination of morphine plus an NMDA antagonist which is optimally effective in preference to an NMDA antagonist alone. We have adopted this approach in our patients. While central sensitisation and wind-up are distinct phenomena, both respond to NMDA and the clinical correlates of allodynia, hyperalgesia and hyperpathia have been the keystone of our assessment tools.[22]

Aim

The aim of this study was to establish the safety and efficacy of ketamine in a cohort of patients with pain of malignant origin and physical signs of wind-up, which had not responded to morphine along with use of appropriate adjuvant analgesics.

Methods

Consecutive patients referred for management of malignant pain were considered for this study which was discussed with the Local Ethics Committee. The unlicensed use of ketamine as an analgesic in uncontrolled pain with no other reasonable pharmacological options was considered appropriate.

All patients considered for ketamine infusion had to be alert and orientated and able to give informed consent. Patients were eligible for treatment with ketamine if they had received a trial of opioid analgesia and adverse effects had limited further titration. A few patients could only tolerate a weak opioid such as codeine or dextropropoxyphene but since their action is also through the mu receptor, these patients were also included. In addition, each patient had a trial of an appropriate adjuvant analgesic(s). Critical hypertension and/or confusion were the main exclusion criteria. All patients had advanced cancer, however only 7 of the 30 patients were in the terminal phase of their illness, i.e. in the last weeks of life.

All patients included had to have two out of three symptoms of: allodynia, hyperpathia or hyperalgesia, in addition to a demonstrated lack of analgesia with morphine.

Any patient who had even subtle signs of opioid toxicity e.g. vivid dreams, had a 25 per cent morphine dose reduction. All patients were converted to quick-acting morphine preparations, given every 4 hours, and as required. Controlled-release preparations were discontinued in case of a sudden increase in opioid responsiveness leading to opioid toxicity.

Adjuvant analgesics were not altered during the period of treatment with ketamine.

Haloperidol, 1.5mg orally (repeated as necessary) was made available for any patient who experienced any side effects to ketamine. The commonest side-effects at these subanaesthetic doses are disassociation from the environment and emotional lability. The majority of the patients, (22), were inpatients and 8 were treated as out-patients in the day ward area with careful monitoring. All patients had baseline blood pressure recorded and then 4-hourly measurements. Twenty patients had subcutaneous infusion (0.1-0.6 mg/kg/hr) of ketamine and ten had intravenous infusion. Intravenous infusion was used for convenience in some patients, particularly out-patients. Both routes are accepted practice. The latter had hourly blood pressure recordings and had the infusion of 30 mg of ketamine over 3 hours. The group receiving intravenous ketamine were all out-patients. All patients had an average pain score over the past 24 hours and pre ketamine and 24 hours post-ketamine pain scores documented.

A recent systematic review by McQuay and colleagues suggest that 'moderate' pain is equivalent to pain over 35 mm on a 100 mm visual analogue scale and severe pain is equivalent to more than 56 mm on a visual analogue scale. In this study responses were noted as none, mild, moderate or severe pain. A positive analgesic response to ketamine was considered if a patient had a two step improvement e.g. severe to mild pain or moderate to no pain.

Results

Thirty patients with pain of malignant origin received ketamine, 18 females and 12 males, aged 16 to 74 years. Nine had sarcoma, 4 cervical carcinoma, and the others a variety of other tumours. Twenty patients had a continuous subcutaneous infusion, dose range, 0.1 to 0.6 mg/kg/hr, (median 300 mg S.C. per 24 hours) and 10 patients had an intravenous infusion, range 30-60 mg (median 35 mg) over 3 hours.

Twenty-one patients had a positive analgesic response to ketamine and 9 patients had no response or no significant response. Five patients who had a response had a reduction in opioid dose.

Four patients had ketamine related psychotomimetic side-effects requiring haloperidol. One man requested the ketamine subcutaneous infusion to be discontinued despite excellent analgesia because of emotional lability. There were no serious side-effects.

Figure 1 illustrates the pain levels before and after ketamine and opioid doses before and after ketamine. The duration of treatment required seems to vary greatly between individuals and ranged from a total of one infusion, either intravenous or subcutaneous, to a weekly infusion over 5 months.

Patients lived from 4 days to 18 months following treatment (mean 5 months). All patients who responded to ketamine appeared to regain responsiveness to opioids, i.e. opioid analgesia was reported as more effective than before ketamine.

Discussion

The improvement in pain sought was large in order to compensate a little for any improvement due to increased medical input and the placebo effect of any drug. While a double blind randomised placebo controlled trial would be a more robust evaluation of the efficacy of ketamine, the observations in this study are nonetheless noteworthy. It seems that an analgesic response, noted in just over two-thirds of patients is associated with improved opioid-responsiveness as reported by patients. From in-vitro and animal work this would be predicted i.e. the NMDA antagonist renews opioid responsiveness by reversing morphine tolerance. Patient selection is important; patients with the clinical correlates of wind-up are an obvious choice. We are running a double blind randomised placebo-controlled trial in patients with pain due to peripheral vascular disease (same NMDA mechanism involved) and neuropathic pain due to malignancy. All patients have access to the active drug if there is no analgesic response within 24 hours of receiving the trial drug. However, collaboration with the pharmaceutical industry to do a double-blind randomised controlled trial with racemic ketamine and single enantiomer

S-ketamine is currently underway. This may have the advantage of producing an oral preparation without psychotomimetic side-effects.

Conclusion

The NMDA antagonists may be crucial analgesics for future development.

Sadly our ability to control cancer pain with opioids and appropriate standard adjuvant drugs is not successful in all cases. At least 50 per cent of all cancer pain of moderate or severe intensity is neuropathic in nature. The clinical difficulty with neuropathic pain is that in many cases the doses of opioids required are incompatible with any acceptable side-effect profile.

We have seen the preclinical evidence for morphine tolerance at spinal cord level due to stimulation of the NMDA receptor. In animals this can be reversed by NMDA antagonists.

In clinical research trying to tease out morphine tolerance is not easy. Some may argue, what is the difference between morphine or opioid unresponsiveness and morphine or opioid tolerance. The answer in clinical practice clearly lies with the patients history and like the assessment of opioid tolerance has to be a retrospective diagnosis. In the case of this study the diagnosis of opioid tolerance is given by a renewed response to opioid analgesia, which in this study must be due to ketamine since no other changes in the patients' regimens were made.

The clinical history of renewed response to opioid analgesia is straightforward and was volunteered by the majority of patients who had improved analgesia following ketamine.

The conclusion I have came to is that as in animal studies, the clinical situation with the NMDA antagonist, ketamine, is as a mediator of renewed opioid responsiveness at spinal cord level. Ketamine reverses central wind-up and hence the clinical correlates, which seem to be poorly responsive to opioids alone. These clinical correlates responded well in two-thirds of patients in this study to ketamine plus opioids.

Clearly the future of NMDA antagonists for all appropriate clinical situations depends on current clinical trials and availability of a more refined NMDA preparation; the oral route is always preferred and failure to produce an oral preparation will bias patient selection. In addition, racaemic ketamine, as used in this study can be associated with unacceptable side-effects. However, this area of NMDA antagonists role in neuropathic pain and central wind-up associated opioid tolerance, is a very important area for future improved analgesia.

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Study No	Opioid Dose Pre-Ketamine 24 hrs	Opioid Dose Post-Ketamine 24 hrs	Ketamine Dose	Ketamine Duration Frequency	Pain Pre Ketamine	Pain Post Ketamine	+ = analgesic response _ = no analgesic response
1	unable to tolerate oral morphine Coproxamol x 8 per day	160 mg morphine	50 mg IV every week	16 weeks	Severe	None Comes back after 1 week	+
2	unable to tolerate codeine	Cocodamol x 6/day	40 mg IV every 3 weeks	13 weeks	Severe	None lasts 3/52	+
3	unable to tolerate more than 4 Coprox.	Coproxamol x 6	30 mg IV weekly	1 week	Severe	None/Mild	+
4	Morphine 60 mg unable to tolerate more	880 mg morphine	600 mg S.C./24 hrs (200-600 mg over 1/52 total x 3/52	initially repeated after 6 weeks, last infusion 5 months ago	Severe	None/ Mild	+
5	Morphine 60 mg	880 mg morphine	30 mg IV every 48 hrs	x 3 doses	Severe	Mild	+
6	Morphine 160 mg	Morphine 160 mg	30 mg IV (only received 15 mg)	Once	Severe	Mild/Moderate	+
7	Morphine 900 mg	Morphine 150 mg	200 mg S.C. x 48 hrs	Once	Severe	Mild	+
8	Morphine 300 mg	Morphine 300 mg	300 mg IV 2 weekly	Once	Severe	Mild	+
9	Morphine 800 mg	Morphine 800 mg	30 mg IV 2 weekly	Twice	Severe	None	+
10	Morphine 180 mg	Morphine 60 mg	200 mg S.C. x 48 hrs	Once	Severe	None	+
11	Morphine 20 mg	0	200 mg S.C. x 24 hrs - 500 mg S.c. x 24 hrs	Once	Severe	Mild	+

Study No	Opioid Dose Pre-Ketamine 24 hrs	Opioid Dose Post-Ketamine 24 hrs	Ketamine Dose	Ketamine Duration Frequency	Pain Pre-Ketamine	Pain Post-Ketamine	+ = analgesic response _ = no analgesic response
12	1000 mg	3200 mg	300 mg S.C. x 2 days	Over 10 months approx. every 3 months	Severe	Mild	+
13	300 mg	300 mg	300 mg S.C./24 hrs x 3 days	Once	Moderate	Moderate	-
14	250 mg	300 mg	350 mg S.C. x 3 weeks	repeated after 9 months	Severe	Mild	+
15	90 mg	120 mg	250 mg S.C. x 4	Died - expected	Severe	Mild	+
16	1200 mg	1600 mg	200-600 mg S.C. x 3 weeks	3 weeks	Severe	Moderate	-
17	(2 gms) 200 mg	2500 mg	200 - 400 mg S.C. x 10 days	10 days	Severe	Severe	-
18	2250 mg	6000 mg	35- - 500 g	1 month	Severe - epidural	Severe	-
19	Coproxamol 8/day unable to tolerate morphine	Coproxamol 8/day	30 mg IV	Once	Severe with recurrence in 3 hours	Mild	+
20	60 mg	60 mg	180 mg S.C./24 hrs x	1 month	Severe	Mild	+
21	2400 mg	1500 mg	150 - 200 mg S.C. /24 hrs	7 days	Severe	Moderate	-
22	5100 mg	3000 mg	250 mg S.C./24 hrs	10 days	Severe	Mild	+
23	120 mg	120 mg	300 mg S.C./24 hrs	2 days	Moderate	Moderate	-
24	240 mg	1020 mg	200 - 550 mg S.C.	5 weeks	Severe	Moderate	-
25	60 mg	60 mg	30 mg I.V.	Once	Severe	Mild	+

Study No	Opioid Dose Pre-Ketamine 24 hrs	Opioid Dose Post-Ketamine 24 hrs	Ketamine Dose	Ketamine Duration Frequency	Pain Pre-Ketamine	Pain Post-Ketamine	+ = analgesic response _ = no analgesic response
26	120 mg	60 mg	200 mg S.C. x	3 days once	Severe	Mild	+
27	600 mg	1200 mg	30 mg I.V.	Once	Severe	Mild	+
28	400 mg	1200 mg	400 mg S.C. x	2 weeks once	Severe	Moderate	-
29	0 was 60 mg patient stopped - no effect	0	200 mg S.C. x	48 hours	Severe	Severe	-
30	60 mg	120 mg	300 mg SC. x	5 days x once	Severe	Mild	+

Chapter 11

Difficulties with research in the area of palliative care

There is a view that scientifically rigorous clinical research is incompatible with the basic tenets of palliative care and the emotive area of experimenting on the dying has been an ever-present deterrent to some. In palliative care the tension between the best possible total care of the whole person and the "greatest happiness of the greatest number" is accentuated. The tension between maximal individual patient comfort and our obligation to gain scientific knowledge and improve the care of future patients is a tangible problem in palliative care research. However, medical progress, inclusive of palliative care progress, has to be based on research. Palliative care is a clinical discipline, therefore this has to be based on clinical research. Clearly I have approached these clinical studies with the clear intention of not compromising best possible care in any way.

Apart from the moral and ethical difficulties which have to be assessed carefully and are clearly far from uncomplicated, there are the enormous practical difficulties of doing research with a patient group who have multiple problems which are constantly changing and/or evolving. In addition, there is the obvious problem of high attrition in all palliative care studies and the problem of easy fatigue in those who remain, making any study with heavy patient demands inappropriate.

The practical difficulties in study analysis in this patient group are substantial. The problems include: missing data, poor quality data, changing variables within and between individuals over time. New problems will arise unpredictably, in addition to patients being lost to follow-up or patients dying. Interpretation of the meaning of clinical data in patients with advanced cancer cannot be divorced from sensible analysis of data; these two elements must go hand in hand to an even greater degree compared to patient populations where there are minimal changes apart from in the particular variables under investigation.

It can be very difficult to measure accurately the specific variables under study. This is because palliative care is largely concerned with symptom control – both physical and non-physical – and most symptoms are ultimately

subjective sensations e.g., pain, nausea, breathlessness, fear and many others. The quest to find reliable measures for palliative care is fraught with difficulties. Ultimately each patient has to be his own control.

This thesis

The studies in this thesis all use validated tools, however, the time required to explain these tools to patients is significant and requires revision at each reassessment.

The statistical analysis takes into account missing data and changing variables, in addition to attrition. Hence the use of graphs, several statistical tests, depending on parametric or non-parametric data and quantity of data. Such single centre small number studies as described in this thesis clearly lack statistical power in many aspects, however the descriptive data obtained along with those data which are robust in statistical power, form a fundamental research keystone in this difficult area.

The amount of time and expertise required to gather meaningful data in any palliative care study are overwhelming factors. The missing data and attrition in the studies in this thesis are minimal because all patients were personally recruited and followed by the one researcher (Marie Fallon).

In the studies reported, I interviewed all the cancer patients personally and did all follow-up. This minimised missing data. Unless the researcher is experienced in talking to patients with advanced cancer and understanding their difficulties, it is impossible to convey meaningfully how to complete even the simplest of tools. In addition, subtle changes in symptoms and drugs may be missed by the inexperienced interviewer. The data output is closely related to researcher understanding of this patient population. This is clearly quite a different scenario from laboratory based studies or from clinical studies where there are fewer evolving problems and only a small number of easily measurable variables of interest. It is clear why descriptive data has such a key role in most palliative care research. In this thesis there is a substantial amount of descriptive data, especially in chapters 3 and 4.

The rigorous examination of an area fraught with clinical changes and difficulties is clearly not easy, however there has to be the start of such an attempt. This will hopefully allow a greater understanding of the difficulties of research in the area of palliative care and enable others to move this agenda forward in a sensitive and appropriate fashion.

Chapter 12

How does this thesis help to confront opiophobia: Fear of addiction, physical dependence and tolerance?

How does this thesis help to confront these barriers to cancer pain relief? When used correctly, analgesic drug therapy is capable of relieving pain in more than 90% of cancer patients.[1] In reality, patients worldwide continue to endure pain. There is one main reason: irrational fears about using opioid analgesics. Fear of addiction is fed by outdated knowledge about opioids and the unintended effects of the war on drugs. Consequently, many health care workers as well as patients believe that there is a significant risk of addiction when using opioids for cancer pain.

Fear of addiction among physicians, nurses, and patients has been reported in many places in the world including in North America, Asia, Australia and Europe.[2-11]

The irony is that while health care professionals intend to protect patients from pain, their concerns about addiction, which are unfounded, sometimes interfere with pain management. Patients suffer the consequences.

Inappropriate fear of addiction can be linked to several factors, including legitimate efforts to prevent drug abuse, which typically disregard the important medical use of opioids, the media's preoccupation with only the risks of drug use, widespread confusion about the meaning of "addiction", and health care workers' lack of knowledge about opioid pharmacology.

Confusion between addiction, physical dependence and tolerance

A serious error commonly made by health professionals and the public alike is to use "addiction" to describe physical dependence or tolerance. Addiction is defined only by psychological dependence, i.e., compulsive use of a drug for its mood-altering properties, and continued use despite harm. Physical dependence is a normal physiological consequence of chronic opioid therapy. Tolerance means decreased effects with a stable dose of a drug.

Unfortunately, some medical and nursing textbooks,[12] as well as narcotic control laws[13] have defined addiction as physical dependence, thus mistakenly associating addiction with pain management.

Despite significant advances in knowledge about the use of opioids for pain, many healthcare professionals prescribe, dispense, or administer opioids inadequately. There is also a misconception among patients, the public and some healthcare providers that opioids are "bad" drugs because they are often if not always associated with drug addiction and criminal activity. However, studies have shown that opioids used appropriately for pain management are effective, safe, and have an extremely low potential to produce addiction.

The safety of opioids' long-term use has been well documented.[14] Opioids are remarkably safe compared to many other medications. The most prevalent and potentially serious side effect of long-term opioid use is constipation. On the other hand, chronic use of non-opioid analgesics can cause stomach, kidney and liver damage. Patients fearing addiction must be reassured that opioids are safe.

Improving relief of cancer pain in the world will depend in part of eliminating irrational fears of addiction to opioid analgesics. Health professionals should be the first to overcome their fears, so they can educate patients and families, as well as regulators and policy makers. Information about opioids and the true nature of addiction should become part of health professional education to undo the confusion and misinformation which have made fear of addiction the number one impediment to the medical use of opioids, according to a recent survey of governments.[15]

The aims of this thesis were to clarify beliefs in clinical practice about opioid dependence, both physical and psychological, and opioid tolerance. These important and highly topical areas in cancer pain control required clinical research which consisted of a series of inter-related studies.

The process of carrying out these studies was slow and labour intensive, however I feel the data collected is of high quality and attrition and missing data very low because of one researcher. There was no attrition in the bone marrow transplant study, constipation study or ketamine study. Attrition in the psychological dependence and tolerance study was limited to the cancer pain group in the first week because of acute deterioration and death, however all patients who survived the acute symptom period completed the study. While this is not an easy area of research, it is clear that it is possible to carry out clinical research in the area of palliative care.

The major study in the thesis is covered in chapters 3 and 4. The first hypothesis was 'Patients with pain and who use opioid analgesia do not become addicted to opioids'. This had to be investigated using some lateral thinking to try to

tease out any features in pain patients which may be similar to drug addict behaviour. There were difficulties with the use of standard tools which have been developed for the drug addict population, however the use of sensible, clinically-relevant questions redressed this problem. What was clear was that cancer pain patients and chronic non-malignant pain patients both use opioids to relieve pain and are reluctant to stop because of the beneficial analgesia obtained. However, drug addicts use opioids for mood and sleep and are reluctant to stop because of fear of a physical withdrawal syndrome and need to maintain hedonistic effects.

This information is an important start in the process of dispelling myths about opioid use for analgesia leading to psychological dependence. There have been anecdotal reports of safe use of opioids in chronic pain groups, however, no study has examined the issues of psychological dependence on opioids in such a systematic fashion in chronic pain groups and drug addicts at the same time. This study has formed the basis of a much larger study in cancer pain and chronic non-malignant pain patients which also includes the collection of qualitative data as well as the use of the tools described in the initial study. The examination of opioid side-effects versus wanted effects was the basis of chapter 4. The hypothesis was that patients with pain could use the same opioid dose over time and maintain the same degree of analgesia. It is important to show that clinically relevant pharmacological tolerance is not an issue in chronic pain, especially cancer pain management; many patients with cancer pain firmly believe that as their disease progresses and their pain worsens, the analgesic effect of their opioid lessens and they therefore believe that they will die in pain. While our clinical experience tells us that analgesic tolerance is not a clinical issue in cancer pain management, clearly a stronger evidence base is required for such an important question. This study examines opioid use very carefully in the 3 study groups and we see that the pain patients can remain on the same dose of opioid over months, even years, with the same amount of analgesia. On the other hand the drug addicts had to use more opioid to achieve the same level of hedonistic effects. This begins to give firmer evidence for the clinical belief that clinically relevant pharmacological tolerance is not an issue in cancer pain management.

The very process of researching the feared issues of addiction and tolerance to opioid analgesia when used for chronic pain, especially cancer pain, is in itself crucial. This is the beginning of a process of highlighting an important area and starting to tease out some answers to complex questions. As with the psychological dependence study, a larger tolerance study with more patients is currently underway.

The next hypothesis examined in this thesis was to investigate the relationship between opioids and tolerance to their side –effects. We see clearly that the over-whelming association between the common opioid side-effect, constipation, and opioid dose is far from clear and that persistent constipation despite optimal management is strongly associated with poor functional status. This approaches a different aspect of tolerance, is a unique study and is clinically very important. The results of this study are already being put to good clinical use and it has been chosen by the Dannemiller Memorial Educational Foundation as their pain paper of the month.

The thesis then moves on from clinically relevant tolerance, to the examination of morphine tolerance at cellular level in a particular subgroup of neuropathic pain. This is a philosophical link between the larger phenomenon of opioid tolerance and a more specific mechanistic aspect to opioid tolerance in a small subgroup. The hypothesis for this section of the thesis is that overactivation of the NMDA receptor triggers the clinical phenomena of allodynia, hyperalgesia and hyperpathia, and that this can be reversed by using the NMDA antagonist, ketamine. In addition, overactivation of the NMDA receptor can be associated with opioid tolerance and reversal of this or a renewed response to an opioid can be induced by using ketamine. Both parts of this hypothesis did respond to the NMDA antagonist, ketamine. This is crucial clinical research from the point of view of improving cancer pain which does not respond to standard management. Many specialists are already using this information in difficult clinical situations, however I have currently the extreme good fortune to develop my ketamine work further in the form of examining S-ketamine, ketamine and placebo in a double-blind randomised controlled trial. Therefore this work in addition to the other work in the thesis continues to progress.

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